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EDITORIAL

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Year 2020 has been marked by cessation of normal life and adaptation of a new lifestyle in view of the pandemic outbreak of COVID-19. This disruption in activity has affected our schedule too. As a frontline worker, our focus was primarily shifted to formulation and implementation of strategies to cope up with the menace of COVID'19. Owing to these problems, the publication of Journal of Physiology has been delayed by a volume. Hence, this volume of Journal of Physiology is a combined publication of volume XVIII and XIX.

This year we made structural changes in our publication process with setup of a separate editorial office for the purpose of collection of manuscript, making their peer-review arrangements and thereafter publishing the journal on schedule. This process has not only helped us have an independent and impartial peer review process but has also ensured the publication as per schedule.

This year we had included a number of notable personalities in the field as members of our editorial board and enriched the review panel by inclusion of distinguished personalities in the related subjects. As a result the quality of content has increased multiple folds.

In this volume, we have dedicated a separate section to Undergraduate students. Fortunately, the contributions of the Undergraduate students this year were contemporary, related with problems raised by COVID-19. I wish that the contribution of undergraduates will grow further and will fulfil the primary objective of this journal.

One of the achievements of our journal was that it received 225 citations during the year 2018 as per the information available at Index Copernicus. This is a great achievement!

At last, I wish to thank all the contributors, editorial board members and reviewers for their continued cooperation and wish that with their distinguished help the journal will continue to achieve further milestones.

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Original Article

SYMPATHETIC NERVOUS REACTION AND BEHAVIOURAL PROBLEMS IN ADOLESCENTS IN RESPONSE TO DIGITAL DEVICE/ONLINE EXPOSURE

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ABSTRACT

Background: Digital device and excessive online surfing in young adolescents has turned out to be a reason for behavioural disorders among them. We tried to link behavioural disorders in adolescent students with online time spent by them and explored a physiological relationship. **Method**: A total of 312 students aged 13 to 17 years were enrolled in the study. Behavioural assessment of students was assessed by Teacher-rated Child Behaviour Check List (CBCL). All the students were asked for the average online time spent by them in terms of ≤2 hrs and >2 hrs per day. Heart rate of all the students was noted. All the students with behavioural disorders and a total of 30 randomly selected students from those not having any behavioural disorder were selected for the experimental study where they were given access to online digital device use for 30 minutes. After 30 minutes of online exposure change in heart rate was noted and compared between the two groups. Chi-square and Student 't'-tests were used for comparison of data. **Results**: Mean age of students was 15.03±1.44 years. Majority of them were males (57.7%). CBCL revealed behavioural disorders in 43 (13.8%) of cases. Anxiety (n=3; 1%),, Oppositional defiant disorder (ODD) (n=18; 5.8%), Conduct disorder (n=19; 6.1%) and Attention deficit disorder (n=3; 1%) were the reported behavioural disorders. Proportion of those with excessive online exposure (>2 hrs/day) was significantly higher in disordered students (60.5%) as compared to normal students (29.4%) ($p<0.001$). Baseline heart rate was significantly associated with behavioural disorder and online time exposure. Post-experiment change in heart rate was higher in disordered as compared to normal students. **Conclusion**: Excessive online exposure probably affects the brain hormonal levels which bring about physiological changes in heart rate causing behavioural disorders.

KGMU J. Physiol. 2020; XVIII-XIX: 1-5.

Key Words: Behavioural disorders, heart rate, Child behavior check list, Online exposure, digital device use.

INTRODUCTION

The world health organization defines individuals aged 10 to 19 years of age as adolescents. Adolescence is a life stage marked by enormous physical and psychological transformation. It gives the children opportunity to break free from the cocoon environment provided by their parents and to develop their independent thought process. It is a complex maturational and developmental process which varies across individuals and cultures, with successful passage through this portal to adulthood results in physical maturity, a secure sense of self, the ability to enjoy close friendships and group belonging, and the mental capacity to deal with the challenges of the life[1]. It is a life stage where children get to emulate their role models both from real world as well as the fictional world built by stories, television, internet and movies.

Psychosocial adjustment is a hallmark of this phase of development and issues of independence, identity, and relationships define this developmental stage. But, a number of times these growing children fail to manage adequately with the physical, emotional, cognitive, and moral unfolding which leads to a deviant identity and behavioral anomalies[2].

The behavioural changes in the adolescents are influenced by friends, family, teachers and acquaintances. They are also influenced by films, televisions and in the recent years online exposure. Today, teenagers and youths spend a lot of their time on digital devices such as computers, mobile phones and tablets for the purpose of information gathering, knowledge gaining, gaming, chatting, entertainment

and a host of other activities[3,4,5]. Online platforms are unique as they provide unrestricted and uncensored information but at the same time this unrestricted flow of information is inappropriate, especially for young adolescent minds and might influence their behavioural pattern. The excitement and thrill associated with online and offline digital activities like gaming and chatting as well as cyber bullying might also have their own impacts on brain, sympathetic and parasympathetic nervous system which may have a role in behavioural modification of these adolescents[6-11].

Excessive use of digital devices has been shown to result in emotional/behavioral problems among young growing children and adolescents[12]. An Organization for Economic Cooperation and Development (OECD) working paper highlights that excessive use of digital technology has strong effects on brain, cognitive, socio-emotional and physical development of children and adolescents[13].

Excessive exposure to digital devices has negative health effects on sleep, attention, and learning; a higher incidence of obesity and depression; exposure to inaccurate, inappropriate, or unsafe content and contacts; and compromised privacy and confidentiality[14]. The effect of digital device use on physical and mental health has been recognized worldwide. International Classification of Diseases-11 (ICD-11) recognizes gaming disorder under 6C51, supporting the behavioural problems encountered due to internet gaming. In view of the new emerging personality traits and problems in changing technology savvy population, Diagnostic and Statistical Manual Of Mental Disorders Fifth edition (DSM-5) too has placed emphasis on study of emerging measures and models[15,16]. In this study we hypothesize that excessive digital/online exposure in Indian adolescents is resulting in behavioural problems which might be owing to the parasympathetic and sympathetic changes brought about by such exposure that may also affect the brain biochemical balance and in turn affect the behavioural pattern of the adolescents.

MATERIAL AND METHODS

The present study was carried out at a senior secondary school in Sitapur, Uttar Pradesh after obtaining requisite permission from the school authorities and obtaining assent from the participating children. A total of 312 students aged 13 to 17 years studying in standards 9 to 12 were assessed using teacher rated Children Behaviour Check List[18]. Teachers were also asked to enquire about the online/digital device exposure of each student in terms of ≤2 hrs per day and >2 hrs per day. The criteria for >2 hrs was drawn from the study of Agarwal and Agarwal[17] who categorized >2 hrs digital device use by teenager girls as excessive use resulting in ocular symptoms.

On a convenient day, as agreed upon by the school authorities a general health check-up camp was organized in which heart rate of the participant students was noted using a digital pulse oxymeter (Omron CM550N Contec Plus). This assessment was done immediately before the start of second part of study and recorded as baseline heart rate.

In the second part of the study, an experiment was carried out in which all the children having behavioural problems and reporting online/digital device exposure time of >2 hrs/day and a total of 30 randomly selected students without behavioural problems and reporting online/digital device exposure of >2 hrs/day were exposed to online/digital device for 15 minutes without being disturbed or sneaked upon during the period. All the children participating in the experiment were allowed to play their favourite game, chat, blog, watch movie, gather information, visit social networking or entertainment sites, messaging or any other activity as they wished by providing them adequate privacy. After the 15 minutes of online exposure, the students were asked to stop the use of online/digital device. A repeat heart rate measurement was again done through pulse oxymeter within 5 minutes of cessation of online/digital device use.

The difference in post-experiment heart rate and baseline heart rate was recorded as change in heart rate due to online/digital device exposure.

Data so collected was analyzed using Statistical Package for Social Sciences, version 25.0, IBM Inc. Chi-square and Independent samples 't'-tests were used for analysis of data.

RESULTS

Age of students ranged from 13 to 17 years with a mean of 15.03±1.44 years. Majority of students were males (57.7%). A total of 184 (59%) of participants were students of class IX and X while remaining 128 (41%) were students of Class XI and XII. CBCL revealed behavioural problems in 43 (13.8%) students (Table 1).

Table 1: Profile of Study Population and Prevalence of Behavioural Disorders (n=312)

SN	Characteristic	No.	%
1.	Mean Age±SD (Range) in years	15.03±1.44 (13-17)	
2.	Sex		
	Boys	180	57.7
	Girls	132	42.3
3.	Class		
	IX-X	184	59.0
	XI-XII	128	41.0
4.	Behavioural disorders	43	13.8

Among different behavioural disorders, conduct disorder was the most common (n=19; 6.1%) followed by oppositional defiant disorder (n=18; 5.8%), anxiety and attention deficit disorders (n=3; 1% each) respectively (Table 2).

A total of 105 (33.7%) students reported online/digital exposure for >2 hrs per day. However, among those with behavior disorders, the proportion

of those with exposure time >2 hrs per day was significantly higher (60.5%) as compared to that in students without behavior disorders (29.4%) (p<0.001) (Table 3).

Table 2: Types of Behavioural disorders

SN	Type	No. of students	Percentage
1-	Anxiety	3	1.0
2-	Oppositional Defiant Disorder (ODD)	18	5.8
3-	Conduct disorder (CD)	19	6.1
4-	Somatic problems	-	-
5-	Affective problems	-	-
6-	Attention deficit disorder	3	1.0

Table 3: Association between Behavioural Disorders and Excessive Online time spent by the students

SN	Average online time spent by the students	Behavioural disorders (n=43)	No behavioural disorder (n=269)	Total (n=312)
1.	≤2 hrs per day	17 (39.5%)	190 (70.6%)	207 (66.3%)
2.	>2 hrs per day	26 (60.5%)	79 (29.4%)	105 (33.7%)

χ^2=16.06; p<0.001

Table 4: Association of heart rate with excessive online time, behavioural disorders and change following online exposure

SN	Variable	No. of students	Mean heart rate±SD (Range) bpm	Signi-ficance
1.	Behavioural disorders (n=312)			
	Yes	43	84.28±9.66	't'=3.701;
	No	269	79.16±8.22	p<0.001
2.	Online time exposure in overall study population (n=312)			
	≤2 hrs/day	207	78.72±8.19	't'=3.334;
	>2 hrs/day	105	82.10±8.97	p=0.001
3.	Online time exposure in children without behavioural disorder (n=269)			
	≤2 hrs/day	190	78.58±8.26	't'=1.794;
	>2 hrs/day	79	80.54±7.99	p=0.074
4.	Online time exposure in children with behavioural disorder (n=43)			
	≤2 hrs/day	17	80.35±7.40	't'=2.257;
	>2 hrs/day	26	86.84±10.22	p=0.029
5.	Post experiment Change in heart rate following			
	Without behavioural disorders	30	5.03±2.11	't'=4.505; p<0.001
	With behavioural disorder	26	8.55±3.56	

Baseline heart rate was significantly higher in students with behavioural disorder (84.28±9.66 bpm) as compared to that in students without behavioural disorders (79.16±8.22 bpm) (p<0.001). Baseline heart rate was also significantly higher in those having online exposure time >2 hrs/day (82.10±8.97 bpm) as compared to that in students having online exposure time ≤2 hrs/day (p=0.001). Among students having no behavioural disorder, though mean baseline heart rate was higher among those having online exposure >2 hrs/day (80.54±7.99 bpm) as compared to those having online exposure ≤2 hrs/day (78.58±8.26 bpm) but this difference was not significant statistically (p=0.074). However, among those having behavioural disorder, mean baseline heart rate was significantly higher among those having online exposure >2 hrs/day (86.84±10.22 bpm) as compared to those having online exposure ≤2 hrs/day (80.35±7.40 bpm) (p=0.029). Though, an increase in mean heart rate post-experiment was observed in both with and without behavioural disorder groups however, mean post-experiment change in heart rate was significantly higher in those with behavioural disorder (8.55±3.56 bpm) as compared to those having no behavioural disorder (5.03±2.11) (p<0.001) (Table 4).

DISCUSSION

The prevalence of behavioural disorders among adolescent students aged 13 to 17 years was observed to be 13.8% in present study. Using different tools for evaluation, the rate of behavioural disorders in children and adolescents among different Indian studies have been found to range from 9% to 37.6%[19-21]. The prevalence of behavioural disorders in present study is similar to that reported by Gritti *et al*. (2014)[22] who also used CBCL for the purpose and found its prevalence to be 14.7% in school children living in South Italy. As such the prevalence of behavioural disorders among adolescents might be dependent upon not only the tool of assessment but also on a lot of genetic and environmental variables. As far as type of disorder is concerned, in present study ODD and CD were the most dominant problem followed by anxiety and attention deficit disorders. These findings are in agreement with the data of a large population based Dutch Tracking Adolescents' Individual Lives Survey (TRAILS)[23] that indicate that 16% of adolescents are suffering from behaviour disorders, with almost equal rates for oppositional defiant (8.9%) and conduct disorder (8.6%); about 4.2% had attention deficit disorder.

In present study, more than one third (33.7%) students had online exposure >2 hrs. It is not an abnormal finding as high usage of digital/online devices has been reported in various Indian reports, even reporting upto 9 hrs/day of such use among teenagers[3,4]. Agarwal and Agarwal[17] in their study reported >2 hrs/day of digital device use might result in ocular symptoms. In present study, an association between behavior disorders and digital/online exposure time was also observed (Table 3; p<0.001).

The effect of excessive digital/online exposure on physical and mental health of adolescents has also been reported in previous studies too[8-11,17].

In present study, we also evaluated the physiological impact of online/digital device exposure in terms of baseline heart rate and change in heart rate immediately after exposure to digital/online media. We found that mean heart rate of students with behavioural disorder were significantly higher as compared to that of students without behavioural disorder. This is a key issue showing an interaction between hormonal balances in brain and its physiological impact on heart rate. It might be recalled that nervous system plays an important role in maintenance of heart rate. The sympathetic nervous system (SNS) releases the hormones (catecholamines - epinephrine and norepinephrine) to accelerate the heart rate. The parasympathetic nervous system (PNS) releases the hormone acetylcholine to slow the heart rate. As such functions of both SNS and PNS could be influences by changes in serotonin and dopamine levels in brain[24,25]. The increased heart rate in adolescent students with behavioural disorders were thus indicators of altered serotonin and dopamine levels in brain which influenced not only the heart rate but could also be responsible for inducing behavioural disorders. In present study, the association of increased heart rate in those having excessive online/digital device exposure in overall study population as well as in those with behavioural problems showed the possible role of excessive online/digital exposure(mention correlation r value and p value) as an etiology for alteration in brain hormone balance and subsequent change in heart rate and behavioural problems. The experimental part of this study showed that impact of online exposure on physiological changes was higher in those with behavioural disorders as compared to those without behavioural disorders, thus indicating that the level of alteration in brain hormone balance as a result of online/digital device exposure was variable and might be dependent upon different genetic and environmental variates not taken into consideration in present study.

The present study was an initial attempt to understand the physiological basis of excessive online exposure among adolescents and its impact on their behavioural pattern. Owing to limitations, the experimental part was limited only to those children who reported excessive digital device use. We took only heart rate measurements as the reflective of sympathetic nervous system responses. The study could have also enriched if other psychological traits and nervous system responses could also be included. We could also not include sociodemographic profile of students in order to reflect their impact. Despite these limitations, the present study was an attempt to study this problem in a systematic manner, more such studies are recommended to unravel the other studies.

CONCLUSION

Behavioural disorders in adolescents seem to be associated with excessive digital device/online exposure and is accompanied by physiological changes establishing it as a possible etiology.

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Review Article

ROLE OF NEUROTOXICANTS ON BRAIN DEVELOPMENT PROCESS: COGNITIVE AND MEMORY IMPAIRMENT

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ABSTRACT

Environmental Toxicants have been implicated in the pathogenesis of many neurological disorders. It causes learning and memory disorders. Hippocampus and dentate gyrus are two main brain regions which are mostly affected by neurotoxicants. Reactive oxygen species has been also played a detrimental role in neurodegenerative diseases. Exposure of toxicants alters the antioxidant level and increase the lipid peroxidation level. Neurotoxicants disrupt the blood brain barrier and they also played damaging role in blood related disorders. Neurotoxicants are responsible for mood alteration and neuronal dysfunction. This review will focus on the current epidemiological evidence of neuro developmental toxicity in children and adults, with emphasis on memory and cognitive dysfunction. In this study we report that brain development process is considered to be a critical target of environmental neurotoxicants and provide an overview of recent findings of role of neurotoxicants on developmental neurotoxicity and highlight chemicals of concern, beyond traditionally defined neurotoxicants. Finally, we discuss some useful strategies to encounter the toxic effect including the use of rehabilitation, counselling and medications..

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Key Words: Environmental Toxicants, Reactive oxygen species, Neurotoxicants, Cognitive dysfunction, Medications.

INTRODUCTION

Environmental neurotoxicants are known to harm adults as well uniquely sensitive to infants and children's brain. Previous studies show that developing brain is more susceptible to toxins[1,2]. Now a day our environment is contaminated many of new chemicals and these are neurotoxic[3,4]. Neurotoxicants are injurious to health and cause harmful effects on healthy human life. There are many factors of vulnerability in which environmental exposures can interfere with normal brain development and cause neurological dysfunctions. These neurotoxicants alter the nervous system and cause neurological abnormalities. The timing and duration of these exposures during brain development is crucial and can give rise unwanted long-term or permanent neurobehavioral developmental disorders[5,6]. All these abnormalities can have severe disadvantages[7]. They diminish quality of life and cause developmental and learning disabilities, adversely affect the central nervous system (CNS), changes in brain form and function, reduce cognitive and motor skills, with profound consequences for lower social competence[8]. In this study, we will target on the role of some environmental toxicants (Lead, Ethanol, Silver, Cadmium and Arsenic) and also discuss on cognitive and behavioural dysfunction associated with environmental exposures, with an emphasis on human and animal studies.

Lead Exposure

Lead is a heavy metal and it's a known neurotoxic. In mammals, high amount of lead exposure cause anaemia and some other blood related disorders. Lead exposure to children is very harmful and lead poisoning cause learning disability[9-11]. In the past years, lead sugar (Lead acetate) used as a wine sweetener in Roman countries and it's damaged the nervous system and cause dementia[12]. Mental retardation and behavioural disorders are the most

common adverse effects of lead expose in children. Some evidences have reported that certain vulnerable windows like - genetic and environmental factors are also responsible for the detrimental effects of lead on brain development, thereby likely to be exposed certain children more vulnerable to neurological alterations. Glutamate released is reduced from hippocampus due to lead exposure[13-16]. Lead induced neurotoxicity altered the NMDA receptor subunit and affect the neurogenesis process in rat hippocampus[17,18]. High levels of lead exposure inhibit the neurogenesis by activating the protein kinase and blocked calcium channel. Some studies show that Lead toxicity altered the mRNA gene expression in rat[19,20]. Learning and long-term memory process is dependent on neurogenesis. Lead induced neurotoxicity causes adverse effects on learning and memory process. Based on above these studies, we proposed that granule cell neurogenesis and NMDA receptor function is linked together and cause brain impairment. Early identification and treatment of lead poisoning can alleviate the profound and permanent adverse health effects which can protect from long term disability. Keeping the child away from sources of lead could be a very effective treatment. Medications also can be very effective for remove lead from the body and protect the brain from abnormalities.

Ethanol

Several studies reported that alcohol consumption is responsible for alteration in central nervous system. Alcohol induces the cognitive impairment, and cause dysfunctions in behavioural process in children during maternity[21,22]. Low or moderate alcohol exposure cause neurological defects in children during gestation[23-26]. Prenatal alcohol exposure has been implicated in the delayed development and behavioural problems. Age, gender, health condition and some genetic factors are very crucial for significant effect of alcohol on brain development. Hippocampal phosphokinase C and phopholipase C beta 1 is required for learning and its activity is altered by moderate alcohol exposure in rats[27,28]. Alteration in adult hippocampal neurogenesis is linked to hippocampal related learning and memory dysfunctions[29]. Lower to higher concentration of alcohol exposure reduce the hippocampal cell proliferation in adult rats[30]. Moderate alcohol exposure causes neurological dysfunctions in adult[31]. Hippocampal neurogenesis is enhanced by estrogens in adult female rats. Enriched environmental condition is essential for the regulation of some neurotrophic growth factors like nerve growth factor (NGF), Brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF). Ethanol exposure block the neurotrophin receptor in rat hippocampus[32,33], and cause learning and memory dysfunction. Wide research in experimental animals and human subjects are depictive of the effect of alcohol exposure on brain functions. Occupational and physical therapy, and counselling with a mental health professional are effective things that can be beneficial for child to recover from behavioural, emotional, and social problems of alcohol exposure and also to achieve his or her social attainments.

Cadmium

Cadmium exposure interrupts the learning and memory process. Cadmium affect the verbal IQ skills and lower school activities in children[34,35]. Cadmium shows a neurotixicant feature and modulates the neurobehavioral development[36]. Behavioural functions and proper brain function system is altered by low level of pre and post- natal cadmium exposure[37,38]. Zebrafish is a suitable model for the studies of human brain development and neurological disorder like autism because its nervous system development is closely resemble to human nervous system[39]. Cognitive functions like learning and memory is also exhibit in zebrafish[40,41]. Neurogenin 1 (ngn1) is a proneural gene and it initiates the primary neuron in zebrafish and it regulates the motility[42-44]. Neuron differentiation and proliferation is depending on zash1a and zash1b genes functions[45]. During early developmental stage islet-1 gene is expressed and discriminate the motor neurons[46-48]. According to Elly Suk Hen Chow et al.[49], primary neurons present in the brain in the form of cluster during early neurogenesis. Basic helix–loop–helix transcription factors play a key role in the earlier steps of neurogenesis in Drosophila[50] and vertebrates[51] and they are encoded by preneural genes. Neurogenin 1 is functionally similar to Drosophila atonal gene and it play a essential role for initiation of primary motor-, inter-, and sensory-neurons[42]. Cadmium toxicity altered the mRNA gene expression of zash1a and as well as affects the zash1b gene expression. Previous data demonstrated that cadmium exposure altered the ngn1 gene in zebrafish embryo[44,52] and disrupt the learning and memory process. So, cadmium toxicity decreases the proneural gene expression and interrupts neurogenesis process. Maintaining hygiene, and children's keep away from industrial emissions, tobacco smoke and house dust is the best way to safe from cadmium exposure. In line with the present finding, we confer that cadmium exposure at early age may be exacerbate nervous system disorders and has detrimental for brain health. Extensive investigation and study in this area is warranted.

Silver

Silver is most commonly used in medical and consumer products in the form of silver nanopartical and affect on human heath[53-55]. High amount of silver exposure to adult is neurotoxic[54,56]. Silver has a antimicrobial activity and it inhibit the replication, degrade protein function and cause oxidative

damage. Several of developmental neurotoxicant has also same function[3,41,57-59]. Chronic exposure of silver cause neurodegeneration and alteration in neuro behavioural process but high level of acute exposure is not inducing oxidative damage in mice brain. Silver is responsible for developmental neurotoxicity at a concentration dependent manner. Silver induced toxicity cause neuronal deficit in different brain regions specially which is important for neurogenesis. In brain developmental process, silver toxicity cause DNA condensation and it would be interfering with cell replication during the generation of neuronal population[60,61]. Silver induced neurotoxicity induce ROS generation and cause oxidative damage. New cells, which are sensitive to silver toxicity, cause some alteration in neurodevelopment process. Neurodifferentiation is also affected by silver toxicity. While these effects are also occurred in the developing brain, then silver toxicity cause dysfunctions in synaptogenesis process and presynaptic neuron which contain neurotransmitter and attached to different prosynaptic receptor. Higher concentration of silver effects the parameters of cell growth or neurite formation but lower silver concentration did not alter the cell growth parameter and neurite formation. Silver toxicity interrupts in neurotransmitter phenotype through neurodifferentiation. One previous data given the first report on silver toxicity effects which indicates that it is a developmental neurotoxicant[62-65]. Silver exposure at long period can induce brain dysfunction and cell death through brain accumulation. So silver induced toxicity causes adverse effect on human health and its play an important role in neuro developmental disorders.

Arsenic

Arsenic toxicity is a major health concern for hundreds of millions of people globally. Arsenic toxicity via drinking water, and exposure severely affects CNS. Arsenic exposures cause cancer, diabetes mellitus, hypertension, cardiovascular disease and some neurological disorder[66-71]. Arsenic toxicity alters the learning and memory process[72-74], reduce the IQ[75-78], decrease the concentration[79] and attention[80,81] in both children and adults. Several clinical studies show that inorganic arsenic alter the nervous system and cause neuronal dysfunction[82,83]. Free radicals have been implicated as a causative factor for DNA damage, protein degradation, and lipid peroxidation. Arsenic toxicity induces the formation of free radicals[84,85]. Previous data demonstrated that antioxidant enzyme Glutathione reduce the free radical formation[86-88]. Arsenic exposures altered the antioxidants level and produce more free radicals. Previous studies suggest that arsenic may cross the placenta, and exposure affect the utero. Children have a weak defense system of the blood brain barrier (BBB) against toxicity. Therefore, arsenic may easily cross the BBB and affect brain development. Arsenic exposure disrupts endocrine and immune system and also has been shown to alteration in neurotransmitter systems. Therefore, arsenic induced toxicity plays a deleterious effect on neurophysiological functions and show locomotors activity dysfunctions. The published articles suggest that arsenic exposure is severely affect human brain developmental. Current and further prospective birth cohort studies may interpret specific definition of the developmental consequences of arsenic exposure in early stage of life.

TREATMENT

Unfortunately, there are no known treatments of CNS damage related to exposure, although some work is being carried out toward this goal to reverse or cure the effects of neurotoxic damage. In the current scenario, treatment is generally focused on symptomatic and functional disorder present in the individuals. Cognitive rehabilitation and Medications such as brain stimulation therapy may very useful for individual clinical cases, due to neurotoxic insult. Neuropsychological assessment findings can also helpful to support these efforts. A new framework of action much more needs to be prepared to known about the neurotoxic properties. All of these approaches with the hope of someday curing are highly important that will serve as an addon treatment options for individuals affected by these neurotoxic disorders.

CONCLUSION

Several evidences show that many environmental toxicants are a neurotoxicant, and they cause adverse effect on human health can contribute to neurological dysfunction. Environmental toxicants alter the normal brain functions and interrupt the hippocampal neurogenesis. Children are also exposed to unknown neurotoxic chemicals globally, is a major concern that are silently affect intelligence, disrupting memory, truncating social and academic achievements perhaps most seriously in developing nations. In the present review, we explored the effects of some neurotoxicant on memory, learning, social behaviour and motor functions. Environmental toxicants reduce the newly generated cells proliferation. Enriched environment effect on behavioural process, increase learning and memory ability and up regulate the brain functions. Environmental toxicants show a detrimental effect on hippocampal neurogenesis and modulate the structure and function of neuronal circuits. They affect the learning and memory functions and also cause mental disability. Dendrites are also required for neuronal signalling and toxicant exposure change the dendritic morphology as well as alter their functions.

Research also reveals that low socioeconomic status and genetic factors have a more adverse impact on a particular individual defense to neurotoxic effects. Timing and duration of exposure is also important for better characterization of the magnitude and nature of the risks. Some existing interventions show very promising results. According to current

pandemic situation, we have to focus more attention on this issue.

In summary, environmental toxicants are the neurotoxicant and these are very harmful for human health as well as brain development process. They play a detrimental role in new neurons generation, proliferation and survival in hippocampus. Neurotoxic insult can affect children's brain development resulting in poor intelligence quotient (IQ), memory impairment, reduced social activities, and reduced educational attainment. Neurotoxic insult also causes metabolic disorder, high blood pressure, renal impairment, immunotoxicity and affect to every single organ in our body. Neurotoxicants properties needs to be further examine at the cellular level, and thus how it affects brain development. Improved motor coordination, spatial awareness, verbal learning and memory task may be beneficial to recover from neurotoxic damage. More research is needed to develop the strategies that are effective to improve the children's quality of life.
In India, neurotoxicants exposure investigations are at advancing stage rapidly. Some symptoms are often unspecified. In this case, clinicians and specialists both have done a great contribution to recognise the symptoms with multifaceted approach. Proper guidelines for work conditions, more emphasis on safety and health in the workplace and most importantly awareness and education can improve social behaviour and exploratory activity along with restoration of memory impairment, learning and motor functions. Finally, this study presented compelling evidence that the neurotoxicants exposure can result in alteration of learning, memory and social interaction and warrants consideration on the impact of the neurotoxicants on human health with respect to their neurological dysfunction property.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Review Article

MEDICINAL PLANTS IN HUMAN HEALTH: A REVIEW

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ABSTRACT

In almost all the traditional systems of medicine, the medicinal plants play a major role and constitute their backbone. India is enriched with different natural biodiversity and some of which are medicinally important. A numbers of publications suggest the importance of natural products and their importance in treatment. Therefore in this review we discussed the plants which have medicinal properties and these information's are collected from different published manuscripts. Here we discuss in detail about few important plants those have therapeutic effect.

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Key Words: Natural products; Medicinal Plants; Human health; Anti-cancer, Anti-oxidant.

INTRODUCTION

Nowadays a lot of drugs are available in the market to treat ulcer but it is also evidenced that these marketed drugs have a number of side effects too. Then to get over, these adverse side effects, scientists are discovering new molecules which have minimum side effects[1]. That's why the world is searching new molecules from novel sources and their hunt will end after finding the natural products. In addition, it is well known that herbal products have lesser side effects so considering these facts in mind we are focusing on therapeutics agents isolated from herbal products. In this review we tried to collect some medicinal plants that have therapeutic effects.

Some important Medicinal plants that have therapeutic effects

Nyctanthes arbortristis

Common Name: Harsingar

Plant Parts: leaf, seed and flower buds

Distributed Area: Sub-Himalayan regions, southwards to Godavari and Orissa state of India[2].

Active Constituents: The bioactive constituents such as polysaccharides, nyctanthoside, nyctanthic acid, β-sitosterol, 6-hydroxyloganin, 7-O-Trans-cinnamoyl-6 α-hydroxyloganin, arbortristoside-A and arbortristoside-B[3] have been reported from *N. arbortristis*.

Nyctanthes arbortristis Linn (Oleaceae) has been also used extensively in Ayurveda, Sidha and Unani systems of medicines. Arbortristoside-A and arbortristoside-B have been reported to possess leishmanicidal[4], antiplasmodial[5], antispermatogenic[6], antiallergic[7], anti-inflammatory[8,9] antinociceptive[9] and analgesic activity[10]. It is evident from the literature and previous investigations that *N. arbortristis* also possesses significant anti-ulcer activity[11].

Xylocarpus molluccensis

Common Name: Pussur and Pitakura

Plant Parts: Fruits, bark and kernels

Distributed Area: Mahanadi deltaic region and in the Andamans[12].

Active Constituents: The bioactive constituents such as xyloccensins, a class of limonoids

Xylocarpus molluccensis (Lamk) M. Roem. (synonymous to Carapa) (Lamk) belongs to the family Meliaceae. Flowering and fruiting time is from June to September. The kernels are used as tonics and for relieving colic. The fruits are used as a cure for swellings of the breast, in elephantiasis, cholera, fever and also used as aphrodisiac[13]. The bark pressings are used to treat fevers including those caused by malaria. A recent review reveals the various biological activities, chemical constituents and other properties

in the genus *Xylocarpus*[14,15]. It also found effective in gastric ulcer[16,17].

Terminalia chebula

Common Name: haritaki (Sanskrit and Bengali), harad (Hindi), harada (Marathi and Gujrati) Karkchettu (Telugu) and Kadukkaya (Tamil),

Plant Parts: Fruits

Distributed Area: All India

Active Constituents: The bioactive constituents such as chebulinic acid

Terminalia chebula is a flowering evergreen tree of the family Combretaceae. Its methanolic and aqueous extracts of the fruits have been reported to exhibit a variety of biologic effects, e.g., antioxidant[18], antimicrobial[19], antianaphylactic[20], antidiabetic[18], anticancer[21] and antiulcer[22].

Peganum harmala

Common Name: harmal'

Plant Parts: Bark, Leaf, Fruits, Seeds, Flower

Active Constituents: The bioactive constituents such as peganine hydrochloride also known as vasicine

Peganum harmala Linn (Zygophyllaceae), different parts are used in traditional systems of medicine for the treatment of variety of human ailments such as lumbago, asthma, colic, jaundice and as a stimulant emmenagogue[23]. From current pharmaceutical studies, several pharmacological activities have been reported for *P. harmala* such as anti-tumor, insecticidal and antimalarial effects[24], wound healing, anti-oxidant activity, immunomodulator properties leukemia healing[25], anti-ulcer[26] hypoglycemic effects[27], analgesic and anti-inflammatory properties, antinociceptive effects[28], antitumor activity[29].

Dysoxylum binectariferum

Common Name:

Plant Parts: Leaf, Stem Bark, Fruits

Distributed Area: India and Southeast Asia

Active Constituents: The bioactive constituents such as Dysobinin, a tetranortriterpenes, Terpenoids Rohitukine—a chromone alkaloid

The genus ***Dysoxylum*** belongs to the family Meliaceae and is used for the treatment of leprosy and foul ulcers[30]. Dysobinin, a tetranortriterpenes isolated from its fruits showed depressant action and anti-inflammatory activity[14]. Terpenoids of this genus were also reported to have anti-tumor, and molluscicidal properties[31]. Rohitukine—a chromone alkaloid—is the major active constituent of stem bark of *D. binectariferum*. Rohitukine have been reported previously for several biological activities including anti-inflammatory, immunomodulatory, anti-cancer[30,32], contraceptive[31] and gastroprotective properties[33]. Another compound, dysobinin, isolated from the ethanolic extract of the fruits of *D. binectariferum* possesses central nervous system (CNS) depressant and anti-inflammatory activities[34].

CONCLUSION

In this review, we tried to attract the whole world to exploit the beneficial effects of natural products and established a new era for herbal medicine. Keeping these facts in mind scientists and researcher are focused on new molecules from natural sources. We also tried to highlight the role of natural products in human health. We appalled when we saw the several medicinal plants have notably medicinal property and have lesser side effect so it may be act as a candidate molecule in near future.

Future plan

Consequently developments of new and novel molecules from natural products are best strategy in the genesis of new drugs. In addition we are focusing on herbal molecule which opens new window in the field of drug discovery program.

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Review Article

ROLE OF ENVIRONMENTAL CONTAMINANTS IN DEVELOPMENT OF DIABETES: A REVIEW

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ABSTRACT

Diabetes mellitus, often referred to as 'diabetes', is a universal health problem, now growing as an endemic. Diabetes is mainly of two types, type 1 diabetes, which occurs mostly in children and young adults, and type 2, which usually occurs in adult patients. Impaired insulin functions are common features in both types of diabetes. Previously, physical inactivity or an unhealthy diet were thought to be responsible for diabetes, but some studies suggested that diabetes is a multi-factorial disease and that both genetic and environmental factors may be responsible for the development of diabetes. Some studies have also proved that environmental toxins such as endocrine decomposing chemicals, pesticides, heavy metals, persistent organic pollutants, etc., act as an initiator to develop diabetes. However, there are strong experimental indications that some pollutants affect processes that are related to diabetes development. Some studies also found that people who exposed to higher levels of noise pollution are more prone to diabetes. Hence, through this review we are presenting evidence that suggests that environmental pollutants are also an important link in the development of diabetes and metabolic disorders. Thus this review provides a brief summary to help and support to find out the possible link between this environment and T2DM.

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Key Words: Diabetes; Environment contaminants; Heavy metals; Pesticides; Pollution.

INTRODUCTION

Diabetes is a universal health issue afflicting many people and is also the main cause of death of more than 1.5 million people every year[1]. Diabetes cases have progressively increased over the past few years and as per the World Health Organization (WHO), over 400 million people globally suffer from diabetes, most of which are from developing countries. In the starting of 21st century, India (about 32 million), China (about 21 million) and the United States of America (about 18 million) were the countries with the most number of diabetes cases. According to WHO, it is believed that according to 2015 figures in India, around 70 million population afflicted from diabetes[2,3]. Our knowledge of the factor behind diabetes is incomplete and limited only to lifestyle, unhealthy diet and heredity[4], but of course some epidemiological data also indicates that environmental agents are also the main causes to pathogenesis of diabetes.

Several reports indicate that due to uncontrolled industrialization, a broad sector of the human population being exposed to environmental contaminants that have potential to causes diabetes[5, 6]. Some in silico studies have also shown a link between toxic chemicals and metabolic diseases such as, between the dichlorodiphenyltrichloroethane (DDT) and type II diabetes[7] and also among persistent organic pollutants (POPs) and metabolic diseases[8]. Since knowledge of the researchers about this area is incomplete or not fully explored therefore environmental factors are rarely considered to be the cause of metabolic diseases. Thus, potential factors and their mechanisms need to be explored that can induce hyperglycemia or diabetes. Therefore, the goal of this organized review is to analyze the available literature on environmental pollution and their role in diabetes progression.

Diabetes and its types

Diabetes is described as presence of high blood sugar with disorder in the metabolism of fat, carbohydrates and proteins[9]. It has classified into 3 major types**.** The first category is Type 1 diabetes mellitus which represents about 10-15% of all diabetes cases. Auto immune damage of pancreatic beta cells occurs in type 1 diabetes which causes

insulin deficiency resulting high blood sugar[10,11]. Ultimately, all type 1 diabetes patients will require insulin therapy to maintain glucose levels. The second category is type 2 diabetes or non-insulin dependent diabetes (NIDM), comprising 80% to 90% of all DM cases. Generally, type 2 diabetes patients usually exhibit obesity, which is related to the presence of insulin resistance[12,13]**.** And the third type is gestational diabetes, in which blood sugar levels raise during the period of pregnancy, which usually goes away after giving birth. Based on population studies, it has been observed that GDM affects about 3–9% of pregnancies[14].

Pathophysiology of type 2 Diabetes

In the progression of diabetes, many pathological processes are involved. Insulin resistance and defective insulin secretion cause hyperglycemia that aids in the pathogenesis of type 2 diabetes[15]. At the tissue level, the effect of insulin resistance leads to a decrease in insulin-dependent uptake of glucose in adipose tissue and muscles. In adipose, insufficiency of insulin provokes the hormone-sensitive lipase resulting in a massive breakdown of fat stores in it. Thus an excessive breakdown of triglycerides in the adipose tissue leads to increased circulating FFAs. FFAs not only compete for glucose during metabolism, but their rise is associated with loss of pancreatic b-cell function. In chronic diabetes lipid metabolism is adversely affected. Apart from hyperglycemia, insulin resistance, hyperlipidemia accompanied with the decreased level of HDL potentially contributes to generating lipotoxic effect (lipotoxicity) in diabetes[16,17]. The knowledge of the actual cause of diabetes is still incomplete and unclear but it is speculated that it may be because of some interactions between genetic level and environmental agents. Here, through this review, we have tried to draw attention to the link between environmental pollution and diabetes.

The link between Environmental factors and diabetes

It is believed that interaction of environmental, biological, behavioural and genetic factor may cause diabetes. Literature proposed that environment is responsible to increase risk factors of T2DM by enhancing behavioural, psychosocial and physical stressors[18,19]. Considering on epidemiological figures and in vivo rodent studies, it is hypothesized that diabetes is associated with environmental endocrine-disintegrating compounds (EDCs)[20,21]. However, there are strong experimental indications that some pollutants, such as bisphenol A[22] and certain persistent organic pollutants (POPs)[23], affect processes that are related to diabetes development. Some studies have also believed that people who exposed to higher level of noise are more susceptible to diabetes[24,25]. Here, through this review, we are trying to summarise some evidence of clinical or experimental studies which proofs that environmental factors or contaminants may contribute to initiating or advancement of diabetes.

Air pollutants

Uncontrolled industrialization is a prime cause of air pollution that poses the greatest environmental risk to human health. The WHO said in its report that the effect of air pollution is likely to be stronger in developing countries given the rising levels of air pollution[26,27]. Several authors have concluded in their reports by epidemiological and clinical data that the risk of type 2 diabetes mellitus is also associated with contact to air pollution, and those data also indicate that the relationship between air pollution and diabetes is due to traffic-related pollutants complications such as toxic gaseous, nitrogen dioxide, tobacco smoke and particulate matter etc[28,29,30]. Possibility of diabetes was also associated with traffic related air pollution was reported by Kramer et al (2010) in his study[31]. Further this was also confirmed by Sorenson et al in 2013[32], Andersen et al, in 2012[33] and Heidemann et al (2014)[34] in their study. They found that there was a statistically considerable positive association between continuing exposure to traffic noise and diabetes risk. Sun Q et al, (2009) demonstrated by their experiment that PM2.5 exposure increases insulin resistance and intestinal inflammation / fat exaggeration. They subjected C57BL / 6 mice high-fat feed to concentrated ambient PM2.5 or filtered air for 24 weeks in their experiment and confirmed that mice with PM2.5 showed insulin resistance with increased vascular dysfunction abnormalities[35]**.** Thus, their discovery confirms and delivers new perceptions into the potential role of PM2.5 in the development and pathogenesis of diabetes. In one of study done by Coogan et al (2012) in women, assessed the risks of incident hypertension and diabetes mellitus associated with exposure to fine particulate matter (PM2.5) and nitrogen oxides (NOx), a marker of air pollution cause by traffic, in his study he proves that air pollutants associated with traffic can increase the risk of type 2 diabetes mellitus[36].

Persistent organic pollutants (POP's) and Endocrine disrupting chemicals

Pesticides are one of the main factors of environmental pollution which was believed to be related to neurotoxicity, but some studies indicating that pesticides can also induce metabolic diseases including obesity and type 2 diabetes[37,38,39]. Organophosphate pesticides hit neuron connections via jamming acetyl cholinesterase (AChE) activity as well as this can also cause pancreatitis, which can cause beta-cells to be damaged[40]. Malathion, a specific insecticides that is used as a pesticide in agriculture, has also been linked to metabolic

disorders which is described by Panahi et al (2006) in their experiment on mice models[41]. In addition, malathion increases ROS production that has toxic effects on islet mitochondria and leads to apoptosis[42]. Diazinon is a further pesticide also related with some defects in glucose uptake and poor insulin secretion[43,44]. Pakzad et al (2013) reported that the high dose and or with prolonged exposure of diazinon impair glucose homeostasis via oxidative stress[45]. Similar findings have been also reported by Miranda et al (2014) in high fat diets and monosodium glutamate exposed rats[46]. Saldana et al (2007) in their study found that first-quarter pregnant women exposed to agricultural pesticides had twice the risk of gestational diabetes[47].

Persistent organic pollutants (POPs) are chemicals that never degrade and are highly resistant in nature such as organic pesticides that always exist in the environment since they possess their lipophilic quality. It is believed that obesity acts as part of the storage of these pesticides that provoke insulin resistance and possibly lead to diabetes[48-51]. POPs are also known as endocrine-disrupting chemicals (EDCs) because of their ability to inhibit the normal performance of the endocrine system[52,53]. 2,3,7,8 tetrachlorodibenzo-p dioxin (TCDD), polychlorinated biphenyls (PCBs), Diethylstilbestrol (DES), dichlorodiphenyltrichloroethane (DDT) and its metabolites etc are the some general examples of EDCs. Some reviews also emphasize that there is some correlation between EDC exposure and metabolic syndrome like obesity, diabetes etc[54-58]. It is well known that 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD) is the most poisonous substance in all POPs. Some studies showed that exposure from TCDD leads diabetes and insulin resistance[59-62]. Atrazine (ATZ, 2-chloro-4-ethylamine-6-isopropylino-s-triazine), is a extensively used herbicide that is currently associated with the obesity epidemic[63,64]. It has been found that prolonged exposure to atrazine specifically contributes to the progression of insulin resistance and obesity in a rat model of high fat diet[65]. Polychlorinated biphenyls (PCBs) are a manmade compound comes under example of EDCs chemicals that remain detectable in human tissues as a result of their environmental and biological persistence. Several evidence have support this facts and also shown that PCBs are associated with diabetes and also a risk factor for metabolic disease[66-71].

Bisphenol-A (BPA) is another EDC commonly used to make hard plastics and their products and is also associated with metabolic diseases[72,73]. A workshop review based on rodent studies organized by the National Toxicology Program found that BPA can have an effect on glucose homeostasis and insulin secretion[74]. A meta-analysis that included some cross-sectional and prospective studies showed a positive relationship between bisphenol A and metabolic disorder by comparing the highest to minimum risk groups[75]. These outcomes of the studies support a more current meta-analysis of the prevalence of diabetes[76,77]. Thus, based on appropriate evidence we can say that differential BPA risk may promote diabetes heterogeneity.

Phthalates are kind of synthetic compound that is utilized for a multiple purposes[78]. The results of various epidemiologic studies have concluded that diabetes is correlated with high phthalate exposure. A cross-sectional study done by Sun et al (2014), also concluded that exposure to BPA and phthalate metabolites among the middle-aged people could be related with T2D risk[79]. Huang et al (2014) examined the evaluation of diabetes marker and Phthalate metabolites by gender and race/ethnicity their study. The results of this analysis were indicated that some populations may be more prone to phthalates exposure in relation with disorder in glucose metabolism[80].

Heavy metals

In the world, the main reason behind of heavy metal pollution is that industrialization. Researchers suggest that heavy metals negatively affect health and cause many serious diseases[81,82] and also may play a role in the development of diabetes. Several studies have been reported on the association of heavy metals and diabetes[83-86]. In diabetes, oxidative stress occurs by some reactive oxygen species (ROS), which arises due to the imbalance of essential metals[87,88]. A number of studies have found some toxic metals in biological samples of type 2 diabetes patients that adversely affect a person's health status by inhibiting organ physiology and functions[89-92].

Iron (Fe) is an essential metal and main component of two important functional proteins like hemoglobin and myoglobin found in the blood. Fe is transported by a glycoprotein called transferrin into the cells and ferritin is a blood cell protein that contains iron. Jehn et al (2004) in their cross-sectional study showed that increased levels of iron were highly correlated with metabolic syndrome and insulin resistance[93]. Increased level of Fe causes oxidation of various biomolecules present in a body, which could contribute to the development of T2D by reducing insulin secretion from pancreatic beta cells as well as insulin resistance[94]. A number of studies have revealed a strong correlation between serum ferritin levels and insulin resistance[95-99].

Zinc (Zn) is a crucial metal that makes an essential contribution to the deposition and production of insulin, which later increases the uptake of glucose and related with diabetes[82,99,100]. Zn transporter (ZnT8) a group of Zinc protein found in mammals is an regulatory protein for the insulin secretion from the pancreatic β-cells and mutation in ZnT8 transporter has been connected with T2D in recent studies[101,102]. Zinc level in plasma negatively affects the efficiency of islet cells to production or excretion of insulin and it has been linked to the diabetes mellitus in experimental and clinical studies[103-106].

Arsenic is a very toxic semi-metal that causes disorders in nervous system, endocrine disruption and cancer etc, it was also found that arsenic alters certain biological processes that regulate insulin resistance[107]. In Taiwan, Lai and colleagues first time described the link between arsenic exposure and the development of type 2 diabetes, through drinking water[108], and this was later confirmed by several cross-sectional and cohort studies from Bangladesh[109] and Taiwan[110]. Various studies have also indicated that arsenic could alter signalling factors that influence the insulin-stimulated glucose uptake in adipocytes or skeletal muscle cells, which could be possibly related with insulin resistance[111-115].

Cadmium is also extremely toxic heavy metal and also has no beneficial use inside the body[116]. Several studies concluded that cadmium-induced hyperglycemia involves increased lipid peroxidation, insulin deficiency, gluconeogenic enzyme activity, etc.[117-119]. Several studies also revealed that a cadmium level in diabetes mellitus patients were significantly higher than in their respective controls and confirms the relation between cadmium exposure and diabetes[120-123].

Mercury (Hg) is also comes in the toxic metal category, that present in three forms in the environment, including metallic mercury, inorganic mercury (iHg) and organic mercury[124]. Inorganic Hg is changed by microorganisms to methylmercury (MeHg) that is the most toxic form of Hg that bioaccumulates in aquatic food chains[125]. It is well known that increased level of mercury in body induces damage in various cell types, including pancreatic β-cells. Chen et al (2006b) confirms this by their experiments in beta cell isolated from mouse. They exposed β-cell with doses of MeHg of 20 μg/kg during 2 weeks, resulting beta cell dysfunctions which leads hyperglycemia[126,127]. Several epidemiological studies have also established the relationship between biomarkers of Hg exposure and DM or MS development[128-132]. Thus, these observations provide sufficient data to confirm this assumption that mercury is an environmental risk factor for diabetes

Other Toxic Compounds

Inorganic nitrate (NO_3) and nitrite (NO_2) are naturally found compounds in foods and their supplements. Vegetables and drinking water are the major sources of exogenous nitrate, while processed meat and animal food products are the main sources of nitrite[133]. Helgason and Jonasson were the first investigators, in 1981, who noted that nitroso compounds can also cause type 1diabetes in individuals[134]. Various studies have reported that nitrate-nitrite have harmful effects on pancreatic beta cells due to the production of peroxynitrite, reactive nitrogen intermediates, and nitrosamines, in addition few studies have also confirmed that there is a correlation between type 1 diabetes and exposure of nitrate-nitrite[135-138].

CONCLUSION

We have tried to provide evidence that greater exposure to environmental pollutants may be an important factor in the development of diabetes, but there are no clear environmental contaminants in our review that could explain the variation in diabetes rates. In this review, we have described based on scientific reports that various environmental contaminants could be related to a risk of diabetes. Reports on arsenic and TCDD exposure were notable but incomplete with respect to type 2 diabetes, and for type 1 diabetes data on intake of nitrates, nitrites, and a nitroso compounds were less suggestive but not completely invalid. However, no specific clues have been found in epidemiology data from available literature on the role of metals in diabetes but it can be concluded that normal levels of essential metals are disturbed in T2D patients. It can also be understood that normal levels of other metals can also be affected by changes in the level of one metal. Environmental toxicants and their molecular mechanism via they can contribute to diabetes risk would be a relevant area for further study. Collectively, all this information gives clear evidence associating environmental contaminants exposure and type 2 diabetes but further studies are needed to determine the appropriate route of mechanism.

Conflict of interest statement

The authors declare that there is no conflict of interest

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Original Article

ROLE OF L-ARGININE ON VISUOSPATIAL ABILITIES IN PATIENTS WITH COGNITIVE IMPAIRMENT AND DEMENTIA

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ABSTRACT

Background: Cognition comprises of five domains, namely attention, fluency, memory, language and visuospatial abilities. The beneficial impact of L-arg on visuospatial abilities has been observed in few animal studies, but not in human studies. Similar results in our study could pave the way for studies with larger sample sizes and utilization of oral L-arg at initial stages of MCI and postponement of dementia, when possible. Cognitive impairment and the impact of oral L-arg on visuospatial abilities was judged using Addenbrooke's Cognitive Examination-III (ACE-III). *Aim*: To assess the impact of L-arg on the visuospatial abilities domain in patients with cognitive impairment and dementia. *Methods*: The cognition of 38 individuals with complaints of failing cognition was assessed by Hindi version of ACE-III. Oral L-arg and placebo were given to these subjects after double- blinded randomization and allocation concealment. The intervention was continued for 30 days, followed by re-assessment of their cognition by ACE-III. Later after de-coding Group I (oral L-Arginine) and Group II(placebo) were seen to include 16 and 19 subjects respectively, after 3 dropouts. *Results*: Changes in the visuospatial abilities domain post-intervention were not statistically significant in either Group I (p=0.198) or Group II (p=0.338). *Conclusion*: Oral L-arg does not improve the visuospatial abilities in individuals with mild cognitive impairment or dementia.

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Key Words: cognition, L-arginine, visuospatial abilities, ACE-III

INTRODUCTION

Cognition is the capability to learn, solve problems, remember, recall and appropriately use the stored information. It encompasses five domains: attention, fluency, memory, language and visuospatial abilities[1].

Declining cognition is further broadly understood as the clinical spectrums of mild cognitive impairment (MCI) and dementia. While MCI is a pre-dementia stage, dementia is differentiated from it by compromised social and/or occupational functioning which is sufficient to interfere with independence in everyday activities[2]. Both are a global menace to society. Owing to the high rate of progression to dementia among subjects with MCI, finding preventive measures and introducing interventions at an early stage could be of potential benefit.

L-arginine (abbreviated L-arg) is a semi-essential / conditionally essential amino acid with a basic side chain. Free arginine in the body is provided by the diet, de novo synthesis [via urea cycle], and turnover of proteins[3]. A variety of metabolites are generated in the body, with the two major pathways being the nitric oxide synthase (NOS) pathway (where L-arg is converted to nitric oxide(NO) and L-citrulline) and the arginase pathway (where ornithine, urea and polyamines are synthesized)[3]. NO is known to act as a neurotransmitter in the brain; as a mediator of host defense in the immune system; and as an antiatherogenic molecule in the cardiovascular system, owing to its vasodilator properties.

So far, studies assessing the impact of oral L-arg on cognition have primarily been animal studies, performed in mice, cats, and dogs. Most of the

literature available on these attributes the beneficial effects of L-arg on cognition to its metabolite NO acting as a neurotransmitter and having a role in neurogenesis. Some literature also credits the benefits to another metabolite of L-arg: the polyamines, which have been found to play a major role in neurogenesis.

To the best of our knowledge, no such study demonstrating the effects of oral L-arg on patients with cognitive impairment has been conducted on humans in India till date. Therefore the purpose behind this pilot study was to see if similar results would also be seen in humans. Positive results could pave the way for undertaking of studies with larger sample sizes and utilization of oral L-arg on a larger scale at initial stages of MCI and successful arrest of its progress to dementia, when possible.

MATERIAL AND METHODS

Approval from the Institutional ethical committee was taken before conducting the study. We also followed the ethical guidelines according to the Declaration of Helsinki for human research.

It was double-blind randomized controlled trial (a pilot study), conducted from January 2019 to August 2019.

A total of 38 individuals consecutively coming to the OPD (during the aforementioned eight months) with cognitive impairment were recruited for this pilot study after taking an informed consent from each. Hindi literate patients of both sexes, aged 60 and above, with cognitive complaints who scored <=82 on the Hindi version of the ACE-III scale were included; while those aged < 60 years with a history of CAD, psychosomatic disorders, neurological disorders and a history of smoking, tobacco use (in any form), substance or alcohol abuse, excessive caffeine intake and having deranged serum TSH and/or vitamin B_{12} values and /or deranged value(s) on LFTs and KFTs were excluded.

The Hindi version of Addenbrooke's Cognitive Examination III (ACE-III) was used as the screening instrument for cognitive impairment. It was chosen because of a high sensitivity of 95.5%[4], scores having a wide range, less ceiling and floor effects and availability of a standardised Hindi version. It assesses the various cognitive domains of attention, memory, fluency, language and visuospatial abilities and allocates scores of 18, 26, 14, 26 and 16 respectively, hence a total score of 100.

MS Excel was used to create a random character table, and jars of oral L-arg and placebo capsules were assigned codes D and E, and this coding was privy only to the chief investigator. She disclosed this at the end of follow-ups, so that statistical evaluation could be done. Allocation concealment was done while distributing jars to the recruited subjects. Each jar contained 120 capsules each (800 mg powder in each capsule) to ensure daily consumption of 6.4gms (which was the amount of oral L-arg administered daily for 18 months in middle-aged subjects with impaired glucose tolerance and metabolic syndrome in a study by Monti LD et al in 2018 to assess decreased risk of DM)[5]. In our study, each subject was given two jars with the instruction to take a total of 8 capsules – in three divided doses (T.D.S.) of 2-3-3 before all three meals every day, for 30 days. Compliance was ensured with regular phone calls and also by checking the empty jars after the subject's visit after 30 days. Subjects were instructed to stop consuming the capsules in case of any adverse gastrointestinal symptoms. 35 subjects brought back both the empty jars of L-arg capsules after 30 days. After consumption of oral L-arginine/placebo for 30 days, cognitive impairment of subjects was re-assessed by ACE-III. The pre and post-interventional scores on the ACE-III scale were compared and the effects of oral L-arg were observed and analysed statistically using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical analysis software.

RESULTS

The number of enrolled participants was 38, of which 3 were dropouts, who claimed to have experienced adverse gastrointestinal side effects. The remaining 35 subjects remained compliant and responsive as per phone calls, and brought back the empty jars of L-arg capsules after 30 days. It was at the end of follow –ups in August 2019, that the coding was revealed by the chief supervisor and the 35 participants were grouped into Group I (16) and Group II (19) , according to the received intervention of oral L-arg and placebo respectively.

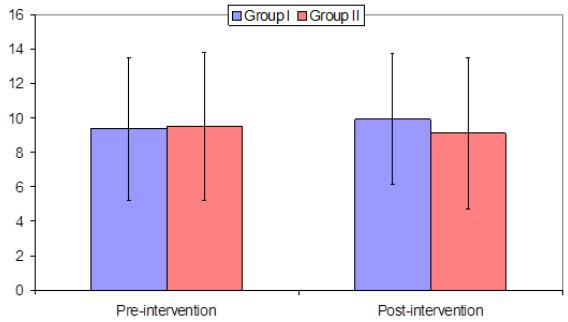

Figure 1: Bar diagram showing inter group and intra group comparisons of ACE-III visuospatial abilities score before and after intervention

Between Group I and Group II, the mean age (p=0.441), gender distribution of study population (p=0.283), educational status of study population (p=0.497) were statistically non-significant.

Pre-intervention mean score of ACE-III visuospatial abilities domain of cognitive function was found to be higher among subjects of Group II as compared to Group I (9.53 ± 4.31 vs. 9.38 ± 4.15), but this difference was not found to be statistically significant. Post-intervention mean score of ACE-III

visuospatial abilities domain of cognitive function was found to be higher among subjects of Group I as compared to Group II (9.94 ± 3.82 vs. 9.11 ± 4.38), this difference too was not found to be statistically significant (Figure 1).

An increment of 0.56 ± 1.67 in pre-intervention ACE-III visuospatial abilities score was observed in Group I while in Group II a decline of 0.42 ± 1.87 in pre-intervention visuospatial abilities score was observed. Percentage change in pre-intervention ACE-III visuospatial abilities score in Group I and Group II were 6.00% and -4.42% respectively. Change in pre-intervention ACE-III visuospatial abilities score was not found to be statistically significant in any of the above groups (Figure 1).

DISCUSSION

A variety of metabolites are generated in the body from L-arginine, including ornithine, citrulline, nitric oxide (NO) aka EDRF, urea, agmatine and polyamines (putrescine, spermine, spermidine). NO generated is either endothelial(eNO), neuronal(nNO) or inducible(iNO)[3].

In the cardiovascular system, NO has been seen to mediate the protective effects of the intact endothelium by acting as a vasodilator and endogenous, antiatherogenic molecule, also known as endothelium-derived relaxing factor (EDRF)[6]. As a neurotransmitter, NO regulates the synaptic plasticity involved in cognitive processes, memory, long-term potentiation (LTP) and long-term depression (LTD)[7] , however, NO is a neurotoxic factor in Aβ-induced synaptic dysfunction and cell death through stimulation of iNOS, but not eNOS and nNOS [8].

Neurogenesis in the adult brain of most mammals occurs from neural precursor cells that are derived from adult stem cells in the subgranular cell layer of the dentate gyrus of the hippocampus and in the subventricular zone of the lateral ventricle[9]. L-arg is involved in different types of cell generation and apoptosis through either the arginase or the NOS metabolic pathways [10].

Arginase controls cell proliferation by modulating the number of neural cells in the S-phase of the cell cycle [11]. It also generates polyamines, which play bivalent functions in neural cell growth and death [12]. Cayre et al.[13] reported that the short-chain putrescine can induce neuronal precursor cells to mitogenesis in adult crickets, thereby increasing proliferation while spermidine and spermine can stimulate neuron differentiation and neurite elongation. On the other hand, eNOS generated via the NOS pathway and VEGF act in a positive feedforward loop[14]. eNOS regulates neurogenesis through a VEGF-mediated manner, while nNOS appears to regulate neurogenesis through a BDNF-mediated manner.

Neuro-inflammation induced by lipopolysaccharide (LPS) has been reported to deteriorate learning and memory. The effect of L-arginine (LA) as a precursor of NO on LPS-induced spatial learning and memory and neuronal plasticity impairment was evaluated by Anaeigoudari A *et al.* [15] in 2015 and it was concluded that administration of LPS impaired spatial memory and synaptic plasticity and LA ameliorated deleterious effects of LPS on learning of spatial tasks. Similarly, it was found by Fonar G *et al.*[16] in 2018 that when arginine was administered intracerebroventricularly in a murine model of AD ,the results showed an improvement in spatial memory acquisition in 3xTg-AD mice.

L-arg has shown a promising role in animal studies. However, this study done by us showed subjective improvements and hence a possible positive impact in the visuospatial cognitive domain of some subjects belonging to the oral L-arg intervention group (Group I), but these results remained statistically non significant. This could be due to small sample size in the study, as well as a short duration of intervention (30 days), so maybe with large sample sizes with long-term duration of intervention, the results achieved could have been statistically significant.

CONCLUSION

This is the first Indian study on humans which concluded that oral L-arg does not improve visuospatial abilities in patients with cognitive impairment.

LIMITATIONS

We had to remain confined to a small sample size of 38 due to scarcity of time, and small turnover of patients with forgetfulness as their chief complaint, when the inclusion and exclusion criteria were strictly adhered to. Also, ACE-III as a screening instrument is lengthy and takes a long time to administer (15-20mins or more, depending on the status of cognitive impairment /dementia of the subject). This was a challenge when it came to irritable patients or those who were recuperating from other medical illnesses (in accordance with our inclusion & exclusion criteria) or those with severe dementia. Moreover, it does not specifically test reasoning and judgment.

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Original Article

RELATION BETWEEN GGT AND WAIST CIRCUMFERENCE IN SUBJECTS WITH METABOLIC SYNDROME WITH NORMAL LIVER FUNCTION

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ABSTRACT

Background: Obesity is an essential component of metabolic syndrome. Obesity has been shown to be associated with oxidative stress too. Gamma-Glutamyl transferase (GGT), an enzyme found throughout the body but most commonly found in liver has been recognized as a marker of oxidative stress. *Aim*: To examine the relationship between GGT levels and Waist circumference in metabolic syndrome. *Methods*: A total of 60 subjects with metabolic syndrome as per NCEP-ATP III criteria having normal liver functions were enrolled in this cross-sectional study. Serum levels of GGT were measured and their correlation was done with components of metabolic syndrome. *Results:* Serum GGT concentrations were significantly higher in subjects with metabolic syndrome compared to those without metabolic syndrome in both genders ($p < 0.05$). Serum GGT was positively correlated with waist circumference (r=0.938; $p < 0.05$). *Conclusion*: These data indicate that GGT and obesity synergistically correlate with the risk of the metabolic syndrome.

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Key Words: GGT, Metabolic syndrome, Waist circumference,Oxidative stress.

INTRODUCTION

Obesity is accepted as a major primary health burden because of its associated complications like Metabolic syndrome, diabetes, cardiovascular diseases, cancer, sleep disorders, renal dysfunction, and infertility etc. Oxidative stress is supposed to play a critical role in linking obesity with its associated complications[1]. Metabolic syndrome comprises of pathological conditions like obesity, hyperglycemia, insulin resistance, dyslipidemia, and hypertension. . Worlwide prevalence of MetS ranges from <10% to as much as 84%, on the basis of region, urban-rural environment, composition (sex, age, race, and ethnicity) of the patient, and the definition used [3-8]. The National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP-III 2001,Revised version 2005 is taken in consideration for selection of subjects with metabolic syndrome in current study.

Obesity is a established principal causative factor in the development of metabolic syndrome[9]. Fat accumulation in excess, has been identified as a major underlying factor in pathogenesis of several diseases including metabolic syndrome, diabetes mellitus, cardiovascular and liver diseases, , all-cause mortality, and a reduced life expectancy [10]. Underlying pathology in these conditions has been suggested to be a attribute of oxidative stress.Other than hepatic fat and inflammation associated with it, one major mechanism in the generation of oxidative stress is the production of cysteinylglycine, which is one of the GSH hydrolysis products produced by GGT, which in turn accelerates the generation of free radicals through its interaction with iron[10]. Several studies have suggested that elevated circulating GGT levels may be considered as markers of oxidative stress and subclinical inflammation, which are conditions inherent to the MS.

GGT is a sensitive marker for hepatobiliary diseases as well as chronic alcohol consumption. Recent studies have shown that elevated serum GGT levels, even within the normal range, could predict development of CVD, diabetes and hypertension, and

it is associated with the risk of MS onset, Irrespective of the individual's alcohol consumption[11,12]. However, the mechanisms explaining the relation between serum GGT level and these diseases are not completely revealed. One possible explanation could be the relation of GGT with oxidative stress.

Link between serum GGT levels and Obesity in terms of waist circumference in this study can help to assess the risk of various cardiometabolic complications associated with metabolic syndrome.

MATERIAL AND METHODS

The present study was a cross-sectional analytical study, conducted in King George medical university, U.P from January 2019 till August 2019. Ethical clearance was obtained from the Ethical Committee of K.G.MU. A total of 120 subjects were enrolled in the study. A total of 60 subjects identified with metabolic syndrome according to NCEP ATP III criteria were included in the study from Clinical OPD of medicine Department KGMU.U.P.

NCEP ATP III modified criteria for the diagnosis of metabolic syndrome.

Dyslipidemia :1) Triglycerides- >150 mg/dl 2)HDL Cholestrol: Men<40mg/dl :Women<50mg/dl

Insulin Resistance : Fasting glucose > 100mg/dl

Obesity: Abdominal Obesity (Waist Circumference) Men >102cm(>40") Women:>88cm (>35").

Blood Pressure >130/85mm Hg

Presence of any 3 or more of the above parameters is considered as Metabolic syndrome.

All the enrolled patients were confirmed for normal liver functions.

Subjects with history of chronic alcoholism or intake of alcohol within 3 months ,liver disease (e.g., acute and chronic active hepatitis, liver cirrhosis), biliary tract diseases, cardiovascular events (unstable angina, myocardial infarction, and stroke), heart failure, peripheral vascular diseases, cardiovascular surgery, malignant diseases, acute infectious, or inflammatory disorders were all excluded from the study. The demographic, lifestyle, medical history, and use of medications of participants were assessed using an interviewer-based structured questionnaire.

Detailed Drug History was taken for each subject and individuals on Anticonvulsants, Oral contraceptives, methotrexate, etc were not included.

Anthropometric assessment: Waist circumference was measured with a flexible and inelastic measuring tape, according to WHO's a recommendation with the subject standing, after a regular expiration, to the nearest centimeter midway between the lowest rib and the iliac crest.

Estimation of Serum GGT

Sample Collection: Fasting (12 hours minimum) Morning samples were taken by venipuncture of antecubital vein, 4ml of the blood sample was collected in a plain vial for liver function test, and GGT estimation. The sample was allowed to clot for 2 hours at room temperature before centrifugation for 15min at 1000*g at 2-8 degrees Celcius for collection of serum. Serum for collective estimation of GGT levels was stored at -20 Degree Celcius. GGT levels were estimated through ELISA Method, by using Elisa Kit, provided by Elabscience.: Human γ GT1 (Gamma Glutamyl Transferase 1) ELISA kit, Catalog No: E-EL-H1012. The kit uses a sandwich – ELISA principle, with a detection range of 1.56ng/Ml and a sensitivity of 0.94ng/mL.

Statistical Analysis

Statistical analysis was performed by SPSS 16.0 version for windows. Data has been expressed as mean ± standard deviation. A 2-tailed P value of <0.05 was considered significant. Pearson's correlation coefficient was calculated to examine relationship between Serum GGT and Waist circumference in subjects with metabolic syndrome.

RESULTS

The age of patients ranged from 30 to 60 years (Mean age 45.50±4.14 years). There were 31 (51.7%) females and 29 (48.3%) males. Mean aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase of patients were 24.24±9.56 IU/L, 25.85±7.65IU/L and 88.05±16.32 IU/L respectively.

Patients were grouped in three groups according to waist circumference, *viz.* <100 cm, 100-110 cm and ≥100 cm respectively with 23 (38.3%), 18 (30%) and 19 (31.7%) patients respectively.

WC Category	N	Mean	Std.Dev	Range
<100cm	23	7.59	1.30	5.19-9.76
100-110 cm	18	12.43	1.55	9.76-13.96
>=110 cm	19	25.27	8.69	15.44-43.67
Total	60	14.64	9.03	5.19-43.67

F=67.02; p<0.001

Table 1: Comparison of Mean GGT (IU/L) among patients in different waist circumference categories

Mean GGT levels were 7.59±1.30, 12.43±1.55 and 25.27±8.69 IU/L respectively among patients with waist circumference <100, 100-110 and ≥110 cm respectively, thus showing a significant incremental trend with increasing waist circumference (p<0.001) (Table 1).

On evaluating the correlation between GGT and Waist circumference using Pearson's correlation coefficient, it was found to be strong and significant (r=0.938; p<0.001) (Fig. 1).

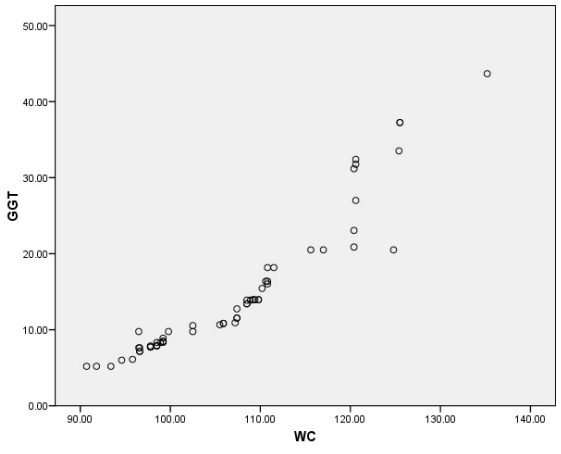

Fig. 1: Correlation between waist circumference (WC in cm) and GGT levels (IU/L) in metabolic syndrome patients

DISCUSSION

Several reports suggest that among the liver enzymes, GGT is the strongest risk indicator for myocardial infarction, stroke, cardiac death[13,14], CAD (p = 0.003) , atherosclerosis, arterial stiffness and plaque and several life-threatening cancers, diabetes, MetS and all-cause mortality. Role of GGT is also documented in increasing risk of mortality in End stage kidney disease patients. GGT is considered as a robust marker of systemic oxidative stress[2]. Some workers also consider GGT as proatherogenic[15].

Metabolic syndrome is a constellation of atherosclerotic risk factors and identifies patients who are at high risk for DM and cardiovascular disease. Serum GGT activity was first reported to be associated with CV disease and all-cause mortality in the British Regional Heart Study.

Considering these associations between GGT and cardiometabolic complications of obesity, In the present study, we have evaluated the possible relationship between serum GGT activity and Obesity in terms of waist circumference in Metabolic syndrome. A study conducted by **Bozbaş H et al[16] in 2011** in metabolic syndrome subjects concluded that serum GGT levels were higher in subjects with metabolic syndrome compared to normal individuals (P=0.008).

This result is in concurrence with the current study .In the present study we have observed a higher level of serum GGT In subjects with metabolic syndrome (Group II) compared to normal individuals (Group I) (p=<0.001). **Bradley R et al [17] in 2013** evaluated the association between total serum GGT activity and metabolic risk factors. They reported a significant association beteeen GGT activity and FBG, HBA1C and BMI.

Various researchers have shown the role of GGT in pathogenesis of diseases like coronary artery disease. **Arasteh S et al[18]** showed that the level of GGT in patients who had >50% obstruction was higher, compared to healthy and patients with less than 50% obstruction in their coronary arteries.An eloquent study **by Drs. Paolicchi and Emdin[11]** at the University of Pisa in 2004 specifically identified GGT in coronary atheroma removed at the time of surgical atherectomy.

Purpose of the present study was to evaluate the Serum GGT levels in metabolic and non metabolic subjects having normal liver function ,Also to examine the relationship between serum GGT levels and risk factors of metabolic syndrome.

We found statistically significant difference (p=<0.001) in GGT values between Group I(non metabolic syndrome) and Group II (metabolic syndrome) , within the normal reference range. That is, GGT values are higher in subjects having metabolic risk factors like hypertension, fasting hyperglycemia, hypertriglyceridemia, low HDL Cholesterol levels and obesity.

In the present study, a statistically significant positive correlation is found between GGT and obese individuals, especially those having abdominal obesity, measured here in terms of waist circumference (Pearson's coefficient =0.938). That is Serum GGT values are increasing in direct proportion to the increase in waist circumference in subjects with Metabolic Syndrome (p<0.001). The INTERHEART study observed a stronger relationship for waist circumference and myocardial infarction suggesting that unfavorable changes in intra abdominal adiposity may be more important in the development of CVD than changes in general adiposity[19].

Adipose tissue produces and secretes many bioactive molecules such as leptin, adiponectin, angiotensinogen, and inflammatory molecules. These adipokines also interact with other tissues and cells in the body that are linked with CVD[20].

Oxidative stress is commonly suggested Underlying Mechanism involved in obesity associated complications like cardiovascular diseases, Diabetes, Liver diseases, Renal diseases. Obesity *per se* can induce systemic oxidative stress through various biochemical mechanisms, such as superoxide generation from NADPH oxidases, oxidative phosphorylation, glyceraldehyde auto-oxidation, protein kinase C activation, and polyol and hexosamine pathways[21].

The presence of excessive adipose tissue has been identified as a source of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6[22]. TNF-α favours the systemic acute-phase response, via the release of IL-6, another pro-inflammatory molecule, and via the reduction of systemic anti-inflammatory cytokines, like adiponectin. TNF-α also increases the interaction of electrons with oxygen to generate superoxide anions [23].

Susceptibility to oxidative damage is even greater in obese subjects because of depleted antioxidant sources, including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), vitamin A, vitamin E, vitamin C, and β-carotene[24].

Compared to normal weight patients, the activity of SOD in obese individuals is reported to be significantly lower[25].

On the other hand, at physiologic serum levels, GGT acts as a protein catalyst in the degradation of glutathione, the major thiol antioxidant in the body.Glutathione is a molecule consisting of glutamic acid, cysteine, and glycine, synthesized within the cell, and may be present both in the reduced state and in the oxidized dimer form by thiol bonding. As an antioxidant, single glutathione molecules are formed and are metabolically inactive and require degradation. One of the products of GSH hydrolysis produced by GGT is cysteinyl-glyceine, which can generate superoxide anion radicals through its interaction with free iron. This effect could promote atherogenesis via LDL oxidation.Unintended oxidization of low-density lipoprotein cholesterol particles may occur, which is felt to participate in the formation of inflammatory atheroma within the vascular endothelial wall[26].

More recently, it has been shown that the oxidants and redox reactions have even wider implications in the diseased vessel wall like smooth muscle proliferation, activities of matrix metalloproteinases and their inhibitors, impairment of nitric oxide production and other functions that have a major effect on atherosclerosis.

An elevation of GGT is seemingly closely related to hepatic steatosis. The latter in turn is strongly associated with the metabolic syndrome. The mechanisms whereby elevated GGT is related to hepatic steatosis have not been determined, but several possibilities have been proposed by Ortega et al[27-29] one of them is that fatty liver could cause hepatocellular damage that would simulate the synthesis of GGT. Alternatively, excess fat in the liver could enhance oxidative stress, leading to overconsumption of GSH with a compensatory increase in GGT synthesis.

Finally, a higher GGT production could be secondary to a low-grade hepatic inflammation induced by hepatic steatosis. It must be noted that high levels of GGT are not the only hepatic biomarker of hepatic steatosis. Elevations of transaminases are common in patients with fatty liver with or without histological evidence of inflammation. Therefore, this can be denied in case of present study as the levels of transaminases are within normal range in subjects of metabolic syndrome and no significant difference is observed in their levels between both the groups.

CONCLUSION

Results of present study show that Serum levels of GGT are raised in subjects of metabolic syndrome and there is a positive correlation between GGT and Waist circumference (Obesity), suggesting that increase in fat accumulation induced oxidative stress can be interpreted through Serum GGT levels and together these two parameters can be used to assess risk of future complications of metabolic syndrome.

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Case Report

A BIZARRE CASE OF A FOREIGN BODY INGESTION

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ABSTRACT

Foreign bodies in the Gastrointestinal tract are not a rarity.But a rat in the gut of a child makes it a rarest of the rare case and one should think of such possibilities if a child comes with repeated vomiting.Timely diagnosis will prevent toxic manifestations and complications.

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Key Words: Rat, vomiting, accidental ingestion, live animal.

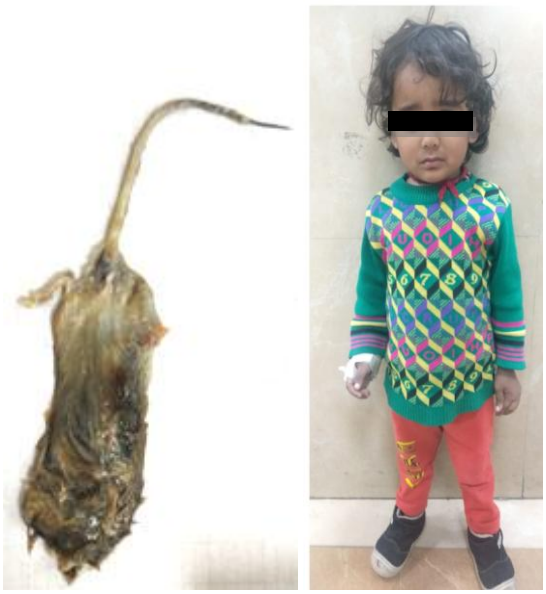
INTRODUCTION

Foreign body ingestion is common occurrence in children with peak age incidence being between6 months to 6years[1,2]. The morbidity and mortality depends on the nature and size of the object ingested.A large variety of foreign bodies are accidentally ingested and can be managed conservatively unless they are causing obstruction and have to be removed gastroscopically. An unexpected foreign body should also be kept in mind in a child who is having recurrent vomiting.

CASE REPORT

A 2 year old male toddler, first born of a well to do family, residing in urban area was admitted to Paediatric ward on 28/1/20 with H/O retching and vomiting since last 36 hours. Vomiting was non bilious, 5-6 times in last 24 hrs, small volume, non blood or bile stained. Before coming to the hospital the parents had already given the child 2 doses of antiemetic, Domperidone but to no relief. At the time of admission the child was conscious, looked restless and agitated. He was retching continuously. He was examined for the same and given one dose of Inj Ondesteron and Pantoperazole. USG abdomen was done to rule out any intestinal obstruction, which was normal. Ten minutes after USG examiation the child had a vomiting again and to every one's surprise a complete dead rat measuring approximately 2 inches in size along with a 3 inches tail, came out in the vomitus.

On retrospective history taking the mother mentioned that the child feeds on the bottle at night and sleeps with his mouth open, and this is how the rat must have slipped into his mouth and got stuck in the oesophagus.



(a) (b)

Fig. 1: (a) The carcass of the rat extracted from vomitus of the child (b) The child who accidentally ingested this rat

The child was admitted and investigated and observed for any adverse reactions related to it, but none were observed during his stay in the hospital for 48 hrs.

DISCUSSION

Foreign bodies in the digestive tract are not uncommon in children. It is common to find button batteries, coins, safety pins being ingested by children. The need to take proper history and analyse for the possibility of foreign body is helpful. Most foreign bodies will pass out without causing damage. Foreign bodies larger than 2.5cm diameter rarely pass through

the lower oesophageal end and be vomited out as such[3]. When a live animal is taken in accidentally or deliberately the stomach acids will burn the skin of most animals and start to digest the muscle and other tissues which may lead to toxic effects or signs of intoxication in some cases[4].

Eating live animals is a traditional practice of humans in many parts of the world. Animals like cockroaches, fish, shrimp, spiders and frogs are also eaten alive for shock value[5,6]. Eating live animals can be fatal too[7]. But this child was lucky not to have any complications due to rapid expulsion of the foreign body.

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Original Article

PREVENTION OF CENTRAL LINE ASSOCIATED BLOODSTREAM INFECTION (CLABSI) AND CLINICAL SEPSIS IN EXTREMELY LOW BIRTH WEIGHT (ELBW) NEONATES FOLLOWING PERIPHERALLY INSERTED CENTRAL LINE (PICC) REMOVAL WITH LINEZOLID

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ABSTRACT

Background: Peripherally inserted central catheter (PICC) line removal can potentially be associated with bacteremia due to dislodging of biofilm especially in extreme preterm neonates. Linezolid can prevent this by acting against coagulase negative staphylocci, the commonest pathogen implicated. ***Methods*:** A randomised controlled trial of neonates weighing less than 1000 grams managed with PICC line to assess the efficacy of Linezolid in preventing Central line associated blood stream infection (CLABSI)/Clinical sepsis in Extremely low birth weight (ELBW) neonates during PICC line removal. ***Results*:** 26 neonates in each group were recruited and analysed. Cohort exposed to Linezolid prior to PICC removal showed no CLABSI and one clinical sepsis compared to single case of CLABSI with five cases of clinical sepsis in the control group (p-0.04). ***Conclusion*:** The trial proved the efficacy of linezolid in reducing the incidence of central line associated blood stream infection in ELBW neonates with added advantage of being safer drug with very less nephrotoxicity in comparison to Vancomycin.

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Key Words: Neonatal sepsis, PICC removal, catheter related blood stream infection, premature neonates.

INTRODUCTION

Peripherally inserted central catheter (PICC) remains one of the essential modes of parenteral access in low birth weight premature neonates due to paucity of veins available for intravenous access[1]. This is more so in sick neonates with respiratory distress and those requiring total parenteral nutrition. Access to central veins have added advantage of giving intravenous fluids which cannot be given through peripheral route due to high concentration of solutes[2].

Due to the presence of biofilm over the catheter which is essentially a foreign body in the central vein, systemic bacterial infections called central line associated blood stream infections (CLABSI) are known to occur[3]. It is postulated that the biofilm which is present on the tip of the PICC line is dislodged during the procedure of removal of the device which leads to bacterial dissemination in bloodstream and subsequent sepsis. This risk has been repeatedly demonstrated in studies involving premature neonates where one study demonstrated almost 2.07-fold rise in culture negative sepsis after PICC removal in neonates less than 1500 grams which increased further to 6.3-fold in cases where PICC was not used to give parenteral antibiotics[4]. These CLABSI are predominantly due to coagulase negative staphylococci (CONS) and other gram-positive bacteria such as *Staphylococcus aureus, Enterococci sp, Klebsiella, E coli*. Some fungal species such as *Candida parapsilosis*are also being increasingly recognised in causing sepsis in preterm neonates and are also implicated in catheter associated infections[4,5]. The ability of CONS to adhere to the surface of central catheter makes it very efficient in forming biofilms and colonising both the surfaces[4]. In developing

countries, gram negative organisms such as *Klebsiella pneumoniae, E. coli*, and *Enterobactercloacae* are also high due to increased bacterial translocation in the gastro-intestinal tracts especially in babies receiving long term parenteral nutrition[6].

Numerous studies have been done to determine the risk associated with removal of PICC line and the effect of parenteral antibiotics during removal of PICC on the subsequent incidence of CLABSI with equivocal results. Recent studies show a definitive protective effect with intravenous antibiotics started before removal of PICC[7-11]. A previous study conducted in this centre indicated protective benefit of antibiotics in extremely low birth weight neonates[12] with predominant organism isolated being coagulase negative staphylococci. Since majority of CLABSI was due to CONS we hypothesized that an injectable anti-staphylococcal antibiotic started 12 hours before removal of PICC should prevent subsequent bacteremia and sepsis in this cohort. Thus, this study was done to assess whether Linezolid demonstrates a protective effect towards late onset sepsis due to CLABSI in extremely premature neonates.

MATERIAL AND METHOD

This prospective randomized control trial was done in a tertiary care hospital for a period of 2 years from Jan 2016 to Dec 2017. It was approved by the institutional ethics committee and a written informed consent was taken from all parents.All neonates born with weight less than 1000 grams not requiring intravenous antibiotics for a period more than 72 hours before removal of an indwelling PICC line were eligible for inclusion in the study. Any ELBW neonate with multiple PICC lines; PICC line placed during an episode of early neonatal sepsis; those requiring continued treatment with intravenous antibiotics during PICC removal; cases with manipulation of PICC or urgent removal for occlusion were excluded. These neonates were randomized by block randomization with the help of computer-generated blocks into two groups: group A with no intervention and group B receiving intravenous Linezolid.

Sample Size

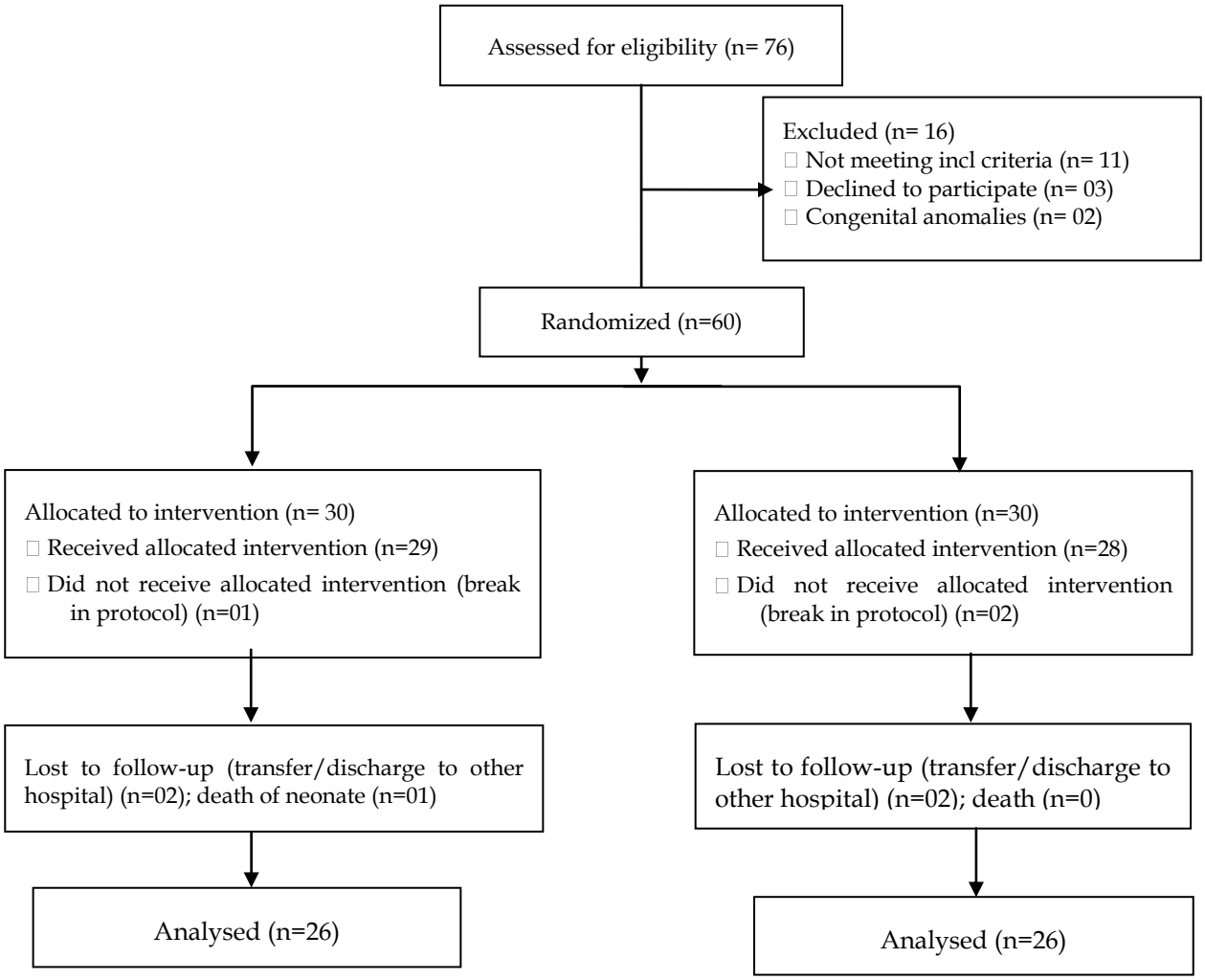
Taking 3% as the average bloodstream infections (BSI) in previous studies[6,7] including one done in this centre[12] with Type I error taken at 1.96 with two-sided test and precision levels at 5%, the minimum sample size comes out to be 22 babies. To cater for drop outs and other losses a sample size of minimum 30 babies in each limb were enrolled.

Methodology

PICC (Vygon 1 Fr, Paris, France) was placed under all aseptic precautions with due diligence in best possible percutaneous vein. Routine asepsis was maintained by dedicated team of nurses. Only topical antiseptic povidone iodine was used for care of insertion site. Povidone iodine dressing were used to maintain sterility of hubs and 3-way stopcocks. These were changed every 24 hours. Heparin infusion in the concentration of 1U/ml were used to maintain patency of catheters in between infusions. No iv antibiotics were used as prophylaxis during PICC placement. No blood products were transfused using PICC.

All the eligible neonates in group B with indwelling PICC during study period were started on Inj Linezolid 10mg/kg/dose in appropriate dose12 hours before removal and continued upto 3 days post removal. CLABSI (CDC-NHSN criteria) was defined as laboratory-confirmed bloodstream infection (LCBI) where central line (CL) or umbilical catheter (UC) was in place for >2 calendar days on the date of event, with day of device placement being Day 1, AND the line was also in place on the date of event or the day before. If a CL or UC was in place for >2 calendar days and then removed, the date of event of the LCBI must be the day of discontinuation or the next day to be a CLABSI[13]. The symptoms defined by CDC for CLABSI in children <1 year include fever (>38°C), hypothermia (<36°C), apnea, or bradycardia.Other researchers have argued to include additional criteria's such as temperature instability, tachycardia, prolonged re-capillarization, metabolic acidosis, and newly developed hyperglycemia[14]. We followed the protocols as recommended by Indian Academy of Pediatrics which suggested clinical features as temperature instability (<36^{o}Cor >38^{o}C), poor cry,lethargy, poor feeding, delayed capillary refill time (CRT) indicating poor perfusion, tachycardia or bradycardia, respiratory distress with apnea or gasping respiration, hypotonia or absent neonatal reflexes and metabolic acidosis[15].Culture negative sepsis was taken as positive sepsis screen in the period of 5 days post removal of PICC with negative blood cultures with any two positive lab criteria comprising sepsis screen. Laboratory criteria for positive sepsis screen were defined as total leucocyte count (TLC) < 5000/cmm, absolute neutrophil counts (ANC) as per Monroe's charts, immature/total neutrophil ratio (ITR) > 0.2, micro-ESR > 15 mm/ hour and C- reactive protein (CRP) > 1 mg/dl[15].

The blood stream infections detected were treated according to our standard treatment protocols with broad-spectrum combination second line antibiotics which was subsequently changed to selective antibiotics as per culture sensitivity reports. Anti-fungal agents were used if indicated by clinical or laboratory criteria or suggested by local skin affliction at the site of catheter insertion. The control cohort was taken as all the ELBW neonates treated in the hospital in the study period who were managed with PICC lines but were not administered intravenous antibiotics during PICC removal. The neonates were randomised into the study and control group with the help of computer-generated randomisation tables. Blinding was achieved by giving normal saline injection in place of Linezolid in the infants of control group.



Data collected before inclusion in study comprised of gestation, sex and birth weight of baby, any major diagnosis, site of insertion, local infection/ inflammation, BSI detected before insertion, total days of indwelling time, presence or absence of early onset sepsis, whether heplock given, total duration of antibiotics given through PICC and when stopped, PICC manipulation and whether lipids were given through the line. Data points during study included evidence of new BSI before removal, occlusion of PICC and sterility practices during handling of the central catheter.

Data Collection

The data for study was collected in pre-designed study proforma and was verified for completeness and consistency before transferring into MS Excel for further analysis. The continuous variables were expressed as mean and standard deviation (SD), median and inter-quartile range (IQR) and frequency distribution for categorical variables. Non parametric tests like Chi-Square and Fishers exact test are applied when necessary. Subgroup analysis is applied between various factors and outcome measures. p-value of < 0.05 was considered statistically significant. Data was analysed using SPSS Version 22.

RESULTS

During the study period a total of 76 neonates with weight less than 1000 grams were identified who required at least one PICC line for the management during NICU stay. Of these 16 were excluded from study due to various factors. 11 neonates did not meet inclusion criteria, 3 parents declined to participate and 2 neonates had congenital anomalies. Remaining 60 neonates were randomised equally to study and control groups. In the study group one neonate did not receive intervention due to break in protocol and 02 neonates were lost to follow up due to transfer/ discharge to other hospitals and 01 neonate died with PICC in situ. In the control group break in protocol was noticed in 02 neonates and 02 babies had to be discharged/ transferred to other hospitals.

The median gestational age of study cohort was 191.81 days (SD 6.4) and birth weight was 881.8 grams (SD 36.7). Average PICC indwelling time was 13.3 days and 21 neonates (80.7%) were given parenteral antibiotics in addition to TPN and lipid infusion. The parameters in the control group were similar with average gestational age 193.92 days (SD 6.1) and birth weight of 897.6 grams (SD 31.4). The average PICC indwelling time was recorded to be 12.7 days (SD 2.3)

and a total of 20 neonates (76.9%) were found to have been given intravenous antibiotics through PICC lines. The difference was not significant statistically with p-values of 0.23; 0.1; 0.33 and 0.35 for gestational age, weight, indwelling time and duration of parenteral antibiotics [Table 1].

Table 1: Clinical characteristics of neonates with PICC

Parameters	With Linezolid	Without antibiotics	p-value
Gestational age (days)	191.81±6.4	193.92±6.1	0.23
Birth weight (grams)	881.8±36.7	897.6±31.4	0.10
PICC placement day	1.4±0.4)	1.5±0.3	0.31
Indwelling time (days)	13.3±2.1	12.7±2.3	0.33
Antibiotics through PICC (%)	21 (80.7%)	20 (76.9%)	-
Mean duration of antibiotics	8.8±1.1	9.1±1.2	0.35

Table 2: Clinical sepsis and Blood Stream Infection

	Type	With Linezolid	Without antibiotics	p-value
1	CLABSI	0	1	0.04
2	Clinical Sepsis	1	5	(CI - 0.028 to 38.48)
	Total	1/26	6/26	

In the cohort of neonates given Linezolid (N=26) started 12 hours prior to removal of PICC, there were total of 1 case of clinical sepsis with negative blood/ CSF cultures and no cases of CLABSI. In contrast 01 case of CLABSI and 05 cases of clinical sepsis were noted in control cohort [Table2].The clinical sepsis was treated with 07 days of iv Piperacillin-Tazobactam with Gentamycin as per the local NICU protocol.CLABSI episodes in the affected neonates were treated with 14 days of iv antibiotics with same protocol.

DISCUSSION

Very low birth weight neonates are nurtured in clinically sterile environment of modern NICUs as they are susceptible to pathogens from the environment. Biofilms adherent to the central lines are also a potential cause of infection in these neonates. CLABSI and culture negative sepsis following PICC line removal can complicate the clinical course of ELBW preterm neonates leading to significant morbidity and mortality. In most cases of CLABSI and culture negative sepsis the common pathogens found are skin commensals especially coagulase negative staphylococcus aureus which was found to be highly efficient in producing biofilms over indwelling catheters. It has been seen in previous studies that these neonates benefit from a course of parenteral antibiotics started atleast 12 hours prior to the removal of the lines with demonstrable reduction in the incidence of both culture positive and negative sepsis[5,6]. The odds of VLBW neonates for contacting culture negative sepsis has been demonstrated to be almost 2.07 folds compared to neonates with weights more than 1500 grams[4]. This effect is all the more pronounced in extremely premature infants when the lines were not used to give antibiotics[6]. Hence this cohort was taken in this study to increase the sensitivity and study the protective effects of antibiotics following PICC removal in the group most susceptible to these infections.

This study was done to determine whether a course of bacteriostatic antibiotics against most common offending pathogen Coagulase-negative staphylococcus aureus (CONS) can prevent against sepsis due to removal of PICC lines. It was done prospectively over a period of two years where all eligible cases in study group were exposed to linezolid prior to removal of PICC and the results obtained were compared to the cases in the control group. Both the cohorts were found to be comparable with respect to the gestational age, birth weight, PICC placement days and the indwelling time of the lines. The cohort not given any antibiotics prior to removal of PICC lines in ELBW neonates showed a definite trend towards both blood stream infection as well as culture negative sepsis. The only case of CLABSI in the control group was due to CONS and was associated with PICC line not exposed to parenteral antibiotics.This finding was comparable to the study done by Casner et al which also showed a definite trend towards culture positive sepsis in neonates not exposed to antibiotics through the PICC line[4]. In contrast, no cases of blood stream infection found in group of ELBW neonates given linezolid. 05 cases of culture negative sepsis were also found in the control group ascompared to 01 case in group exposed to Linezolid.The p-value of comparison of total infections in both groups was found to be significant at 0.04.

According to a Cochrane review done by Craft et al in the year 2000, preterm neonates with PICC lines exposed to Vancomycin prior to removal decreases the incidence of central line blood stream infections[12]. In a systemic reviews done by Lodha et al and Taylor et al, it was concluded that prophylactic Vancomycin decreased the incidence of catheter related blood stream infections, though there is added risk of promoting antibiotic resistant strains[8]. In addition, other studies[10] show beneficial effects of using antibiotic lock in central line forreducing catheter colonization and associated sepsis. A prospective randomised controlled intervention study done by Hemels et al in 2011 demonstrated that central line associated sepsis can be controlled with other anti-staphylococcal antibiotics[11]. This study showed that it is possible to reduce the incidence of CLABSI and culture negative sepsis with the use of Linezolid to a significant extent. Since it is easier to administer and inherently safer compared to Vancomycin with less

nephrotoxicity, it indicates a definitive advantage in the elimination of line related sepsis in NICUs.

Since ELBW neonates in a single centre were recruited for the study, the results may vary for different centres. A multicentric randomised trial will add to the veracity of the results. Another limitation of the study as that different centres in developing countries show an ascendant pattern towards PICC line colonisation with gram negative organisms in which this antibiotic would be ineffective

CONCLUSION

To conclude, Linezolid can be utilised to reduce the incidence of central line associated blood stream infection in ELBW neonates. It can be used in a safe manner with inherent added advantage of very less nephrotoxicity compared to Vancomycin.Whether oral Linezolid is equally effective for prevention of central line infections can be studied in further well designed RCTs.

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UNDERGRADUATE SECTION

UG-Original Article

PATTERN OF ONLINE STUDIES IN COVID-19 ERA AND ITS IMPACT ON OCULAR SYMPTOMS IN HIGH SCHOOL CHILDREN

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ABSTRACT

Background and Objective: CoVID-19 has changed the educational system entirely with online education replacing the classroom education. However, despite its benefits this system has impact on physical health too. In this study we explain its impact in terms of ocular symptoms in High School children. **Method**: A total of 130 students aged 15 to 19 years studying in class IX to XII were contacted electronically to provide their responses regarding pattern of their online and offline studies, use of mobile/computer devices apart from study and ocular symptoms during last one week. Presence of any ocular symptom or ≥3 ocular symptoms was noted. Data was gathered using Google forms utility and analyzed using SPSS 21.0 package. **Results**: A total of 84 students responded, however, 11 forms were incomplete and hence the final assessment was done for 73 students. Mean age of students was 16.12±1.32 years. Majority of them were males (54.8%), spent <2 hrs per day for offline study (52.1%), spent 2-3 hrs per day for online study (56.2%) and studied >5 days/week online (52.1%). Use of mobile/tablet, desktop/laptop and both mobile+computer was reported by 32.9%, 32.9% and 34.2% students respectively. Earplug use was reported by 47 (64.4%) and 35 (47.9%) reported spectacle use. Ocular complaints were reported by 54 (74%) students, ≥3 ocular complaints were reported by 23 (31.5%) students. Blurred vision (46.6%), burning eyes (26%) and headache (24.7%) were the three most common complaints. ≥2 hrs online activity apart from studies was reported by 62.6% students. Ocular complaints were found to be significantly associated with use of mobile/tablet (p=0.050) and ≥2 hrs of online activity apart from studies (p=0.035). Presence of ≥3 complaints was significantly associated with >3 hrs of online study (p<0.001), use of mobile/tablet (p=0.041), earplug use (p=0.027) and ≥2 hrs of online activity apart from studies (p=0.008). **Conclusion**: The findings show a high prevalence of ocular complaints in High school students in CoVID-19 era attributable primarily to longer hours of online activity (both for study and non-study purposes) and type of device used (mobile/tablet).

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Key Words: CoVID-19, Online study, Laptop/Desktop, Mobile/Tablet, Ocular complaints.

INTRODUCTION

Excessive online activity and too frequent use of computer and mobile is related with manifestation of ocular symptoms known as computer vision syndrome[1]. The classical definition of computer vision syndrome covers both extraocular (neck stiffness, neck pain, shoulder pain, headache, backache) as well as ocular (tearing, gritty, dryness, redness, sensation burning, blurring of vision, *etc.*) symptoms[2]. It has been reported to affect those individuals who routinely spend hours glued to computer related with occupational as well as recreational purposes[3-6]. Young children and adolescents are at a high risk of developing ocular symptoms owing to high usage of computer, mobile phone and other such devices. Recurrent and prolonged exposure to computer has the potential to cause pathological damage to the retina and sclera too, as they generally utilize light emitting diode (LED) technology. An LED is a complex semiconductor that emits narrow-spectrum light on application of a definite amount of energy. It is preferred over other sources of lighting the digital devices owing to its energy efficient nature. However, despite this energy efficiency and popular usage, it is often criticized for a dominance of blue light band in its spectrum[7-9]. It would be pertinent to mention here that the most harmful component of visible light

consists of blue wavelength (400–500 nm)[10]. Owing to its short wavelength, it is able to pass through the cornea and could be absorbed by the iris or the pupil[11]. The high energy short wave blue light having wave length in the range of 415 to 455 nm has the ability to directly penetrate into the retina and is known to cause irreversible photochemical retinal damage[12]. Owing to these issues, children, adolescents and young adults are often advised to restrict their computer and digital device usage to a minimum.

COVID-19 has seen a paradigm shift in nature of education. It has compelled to shift the focus from class-room teaching to online teaching resulting into increased hours of computer, mobile phone and other digital device usage which are known risk factors for computer vision syndrome related ocular problems. In present study, we made an attempt to study the pattern of online studies in COVID19 era and its manifestation in terms of computer vision syndrome related ocular symptoms in High School symptoms.

MATERIAL AND METHOD

The data for present study was collected during the first week of August, 2020. A total of 130 students aged 15 to 19 years studying in class IX to XII were contacted electronically to provide their responses regarding pattern of their online and offline studies, use of mobile/computer devices apart from study and ocular symptoms during last one week. Google forms were used to gather the data. A total of 84 students responded. However, a total of 11 forms were found to be incomplete and hence, data for final analysis was available from 73 students only.

History of spectacle/contact lens use, use of ear plugs and headphones during mobile/computer use were also enquired. The students were asked to report presence of any of the following ocular symptoms during the last one week:

- Blurred vision
- Burning eyes
- Itching
- Redness
- Watering
- Headache
- Confusion
- Neck pain

Presence of any ocular symptom or >3 ocular symptoms was considered as a significant manifestation of ocular symptoms as a result of computer/mobile device use.

Type of device used for studies/recreation was also noted.

Data was gathered using Google forms and analyzed using SPSS 21.0 package.

Table 1: Student Profile, Pattern of Online/Offline Study and Ocular complaints (n=73)

SN	Characteristic	No.	%
1.	Mean age±SD (Range) in years	16.12±1.32 (14-19)	
2.	Sex		
	Male	40	54.8
	Female	33	45.2
3.	Class		
	IX	23	31.5
	X	28	38.4
	XI	8	11.0
	XII	14	19.2
3.	Average daily time for offline study	38	52.1
	<2 hrs	22	30.1
	2-3 hrs	13	17.8
	>3 hrs		
4.	Average daily time for online study	5	6.8
	<2 hrs	41	56.2
	2-3 hrs	27	37.0
	>3 hrs		
5.	No. of days/week for online study	1	1.4
	<5	34	46.6
	5	38	52.1
	>5		
6.	Device used for online study		
	Mobile/Tablet only	24	32.9
	Desktop/Laptop only	24	32.9
	Mobile/Computer both	25	34.2
7.	Use of earplugs/headphone	47	64.4
8.	Wear spectacles	35	47.9
9.	Ocular complaints		
	Blurred vision	34	46.6
	Burning eyes	19	26.0
	Itching	7	9.6
	Redness	14	19.2
	Watering	17	23.3
	Headache	18	24.7
	Confusion	6	8.2
	Neckpain	11	15.1
10.	No. of students with ≥3 symptoms	23	31.5
11.	No. of students with no symptoms	19	26.0
12.	Average duration of mobile/computer use apart from online studies		
	<2 hrs	20	27.4
	2-4 hrs	32	30.1
	>4 hrs	21	28.8

RESULTS

Mean age of students was 16.12±1.32 years. Majority were males (54.8%). There were 33 (45.2%) females. Sex ratio was 1.21. Majority of students were studying in class IX and X (n=51; 69.9%). Majority of

students spent <2 hrs per day for offline study (52.1%) followed by those studying offline for 2-3 hrs (30.1%) and >3 hrs (17.8%) respectively. With respect to duration of online study, majority (56.2%) used to study online for 2-3 hrs per day followed by those studying >3 hrs per day (37%) and only 5 (6.8%) reporting <2 hrs of online study per day. During a week, majority studied online for >5 days/week online (52.1%) while 34 (46.6%) studied for 5 days/week and only 1 (1.4%) studied <5 days per week. Use of mobile/tablet, desktop/laptop and both mobile+computer was reported by 32.9%, 32.9% and 34.2% students respectively. Earplug/headphone use was reported by 47 (64.4%). Spectacle/contact lens use was reported by 35 (47.9%) students. Ocular complaints were reported by 54 (74%) students. Blurred vision (46.6%), burning eyes (26%) and headache (24.7%) were the three most common complaints followed by watering (23.3%), neck pain (15.1%), itching (9.6%) and confusion (8.2%) respectively. A total of 23 (31.5%) students reported >3 ocular complaints. As many as 19 (26%) students did not report any symptom. Average duration of daily mobile/computer use apart from online studies was reported to be 2-4 hrs by a total of 32 (30.1%) students followed by those reporting >4 hrs (28.8%). Only 20 (27.4%) reported <2 hours of such use (Table 1).

Table 2: Association of any ocular symptoms with demographic profile and online activity pattern (n=54)

SN	Characteristic	Total No.	Any symptoms (n=54)		Statistical significance
			No.	%	
1.	Mean age±SD in years	16.12 ± 1.32	16.01±1.32		't'=1.144; p=0.257
2.	Sex				
	Male	40	30	75.0	χ^2=0.049;
	Female	33	24	72.7	p=0.826
3.	Class				
	IX	23	19	82.6	χ^2=3.341;
	X	28	21	75.0	p=0.342
	XI	8	4	50.0	
	XII	14	10	71.4	
3.	Average daily time for offline study				
	<2 hrs	38	30	78.9	χ^2=3.784;
	2-3 hrs	22	13	59.1	p=0.151
	>3 hrs	13	11	84.6	
4.	Average daily time for online study				χ^2=0.724;
	<2 hrs	5	3	60.0	p=0.696
	2-3 hrs	41	30	73.2	
	>3 hrs	27	21	77.8	
5.	No. of days/week for online study				χ^2=4.924;
	<5	1	1	100	p=0.085
	5	34	29	85.3	
	>5	38	24	63.2	
6.	Device used for online study				χ^2=6.007;
	Mobile/Tablet only	24	22	91.7	p=0.050
	Desktop/Laptop only	24	15	62.5	
	Mobile/Computer both	25	17	68.0	
7.	Use of earplugs/headphone	47	36	76.6	χ^2=0.472; p=0.492
8.	Wear spectacles	35	28	80.0	χ^2=1.269; p=0.260
9.	Average duration of mobile/computer use apart from online studies				
	<2 hrs	20	11	55.0	χ^2=6.728;
	2-4 hrs	32	24	75.0	p=0.035
	>4 hrs	21	19	90.5	

Table 3: Association of ≥3 ocular symptoms with demographic profile and online activity pattern (n=73)

SN	Characteristic	Total No.	≥3 symptoms (n=23)		Statistical significance
			No.	%	
1.	Mean age±SD in years	16.12 ± 1.32	16.13 ± 1.42		't'=0.031; p=0.975
2.	Sex				
	Male	40	14	35.0	χ^2=0.500;
	Female	33	9	27.3	p=0.479
3.	Class				
	IX	23	8	34.8	χ^2=2.401;
	X	28	8	28.6	p=0.493
	XI	8	1	12.5	
	XII	14	6	42.9	
3.	Average daily time for offline study				
	<2 hrs	38	12	31.6	χ^2=0.004;
	2-3 hrs	22	7	31.8	p=0.998
	>3 hrs	13	4	30.8	
4.	Average daily time for online study				
	<2 hrs	5	1	20.0	χ^2=15.35;
	2-3 hrs	41	6	14.6	p<0.001
	>3 hrs	27	16	59.3	
5.	No. of days/week for online study				
	<5	1	0	0	χ^2=0.801;
	5	34	12	35.3	p=0.670
	>5	38	11	28.9	
6.	Device used for online study				
	Mobile/Tablet only	24	12	50.0	χ^2=6.395;
	Desktop/Laptop only	24	4	16.7	p=0.041
	Mobile/Computer both	25	7	28.0	
7.	Use of earplugs/headphone	47	19	40.4	χ^2=4.864; p=0.027
8.	Wear spectacles	35	13	37.1	χ^2=0.990; p=0.320
9.	Average duration of mobile/computer use apart from online studies				
	<2 hrs	20	3	15.0	χ^2=9.548;
	2-4 hrs	32	8	25.0	p=0.008
	>4 hrs	21	12	57.1	

On evaluating the association of ocular complaints with demographic profile and pattern of online/offline studies and recreational use of computer/mobile devices, no significant association of student age, gender, class of study, average duration of daily offline studies, average duration of daily online studies, weekly frequency of online studies, use of earplug/headphone and spectacles was seen with presence of ocular symptoms. Ocular complaints were found to be significantly associated with use of mobile/tablet (p=0.050) and >2 hrs of online activity apart from studies (p=0.035) (Table 2).

On evaluating the presence of >3 complaints with different demographic variables, online/offline study pattern, device type, duration and frequency of such usage and recreational use of computer/mobile, the only significant association as seen with >3 hrs of online study (p<0.001), use of mobile/tablet (p=0.041), earplug use (p=0.027) and >2 hrs of online activity apart from studies (p=0.008) (Table 3).

DISCUSSION

Covid-19 has resulted in a paradigm shift in terms of education pattern from classroom teaching to online teaching. Though online teaching is the rescue to continue education in the situation of lockdown and to prevent spread of COVID-19 yet it has its own burdens too. While long-term implications of online studies can be enumerated as increased risk of obesity and heart disease[13]. It is also known to affect the physical, mental, emotional and social health of students[14]. Excessive computer/mobile exposure is considered to have effect on users' visual efficiency. Mobile and computer users often complain of a high frequency of ocular complaints as a result of digital eye strain[15]. Although during the COVID19 era, the frequency and time of online and offline digital device use has increased substantially, however, there are no studies evaluating the association of such increased usage of computer/ mobile phone in terms of visual symptoms. In present study we made an attempt to study this issue and found that ocular complaints were quite common among students studying online. In present study, except for 19 (26.0%) students, all the others complained of at least one ocular symptom during the last one week. This is an issue of concern. Moreover, as many as 23 (31.5%) students complained of $\geq$3 ocular symptoms during the last one week. In present study the percentage of computer/mobile use for studies and recreational use was 2-3 hrs and >2 hrs in majority of cases, thus showing on an average >5 hrs of such use by majority of students. In the pre-COVID19 era, mobile use of >2 hrs/day was reported by 80% of medical students in a study by Sadagopan *et al.*[16], who reported presence of ocular complaints in 83% of students in their study among medical students. However, in present study we found presence of ocular symptoms in as much as 74% of students in much younger age group which can be owing to the high usage of mobile/computer exposure for online studies and offline/online recreational purposes. In present study, we found a significant association of use of mobile/tablet (p=0.050) and >2 hrs of online activity apart from studies (p=0.035) with ocular symptoms and >3 hrs of online study (p<0.001), use of mobile/tablet (p=0.041), earplug use (p=0.027) and >2 hrs of online activity apart from studies (p=0.008) with presence of >3 ocular symptoms. These findings indicate that the extended use of computer/laptop for study and recreation, type of device being used and earplug use are associated with high prevalence of ocular symptoms among young children. In a recent study conducted among secondary school children, Agarwal *et al.*[17] showed a significant increase in ocular symptoms with increasing duration of digital device use. In their study they also highlighted the significance of night time use of such devices on the visual complaints. In present study, though we did not study the pattern of online/offline computer/mobile exposure in terms of day-time and night-time use as the focus of the study was on online classes in Covid19 era and such classes are generally held in day time only, however, it seems that recreational computer/mobile use and online studies other than regular classes could coincide with night time use resulting in such high prevalence of ocular symptoms and their frequency. Another study[18] conducted among young Indian children aged 11-17 years also showed that electronic device usage by school children, evaluates factors associated with eyestrain. They reported use of digital device by 20 to 50% students in different age groups and found a prevalence of eye strain to be 18% at the end of day after working on digital devices. In present study, the students were continuously and regularly being exposed to such eye strain and such frequent use of computer/mobile for online studies resulted in a high prevalence of ocular symptoms. The pattern of digital device use was also implicated as a risk factor for eye strain by the authors[18] who reported a high prevalence of such strain among those using it while lying down. In present study, we found that use of ear-plug and use of smaller devices (mobile/tablet) instead of no ear-plug and laptop/desktop use apart from duration and frequency of online studies was also significantly associated with ocular complaints and their frequency.

No doubt Covid19 has brought a significant change in our lifestyle, social and economic activities and it is posing more challenges than the symptomatic manifestation as a result of Covid19 infection. Even those adopting all the measures to beat the virus infection by remaining uninfected are at both social, economic, emotional and health related risks. In view of the fact that Covid19 is here to stay with social distancing as a norm rather than a time-being preventive measure, it is hence time to scrutinize the alternate strategies adopted by us in different spheres of life for their impact on health, social and psychological well-being.

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UG-Original Article

CHANGE IN MENSTRUAL PATTERN AMONG MEDICAL UNDERGRADUATES AS A RESULT OF COVID-19 OUTBREAK RELATED ANXIETY

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ABSTRACT

Aim: To study the changes in menstrual pattern among female medical students as a result of COVID-19 outbreak related stress. **Material and Method**: A total of 126 female MBBS students (I-IV semester students) on forced vacations as a result of COVID-19 outbreak and subsequent lockdown studying in different medical institutions across India were contacted telephonically or through e-mail between July, 2020 to August, 2020. They were enquired regarding changes in menstrual pattern during the lockdown period (March 23 to June 30). Level of anxiety was evaluated using Hospital Anxiety and Depression Scale (HADS). Data was analyzed using SPSS 15.0. Chi-square test was used to compare the data. **Results**: Mean age of girls was 20.29±1.88 yrs. Almost half (49.2%) were below 18 yrs of age. A total of 49.2% (n=62/126) reported of disturbance in menstrual pattern. A total of 12 (9.5%) reported of heavy bleeding, 31 (24.6%) reported fluctuation in interval between two menstrual cycles (short / prolonged), a total of 11 (8.7%) reported of fluctuation in length of menstrual cycles (short / prolonged) while 8 (6.3%) reported of scanty flow. On administration of HADS, 53 (42.1%) had scores indicating abnormality. A total of 23 (18.3%) had significant anxiety while 30 (23.8%) had borderline anxiety. Prevalence of anxiety was significantly higher in girls experiencing changed menstrual patterns (69.4%) as compared to those having normal menstrual pattern (13.7%) ($p<0.001$). **Conclusion**: The findings of the study showed that COVID-19 is responsible for a high prevalence of anxiety among female MBBS freshers which has a physiological impact on the menstrual pattern too.

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Key Words: COVID-19, Menstrual disturbances, Anxiety, MBBS Girl Students.

INTRODUCTION

The effect of covid-19 has not been limited to the direct symptoms associated between it. COVID-19 has affected the human life in more than just having symptomatic manifestation. COVID-19 has changed the entire lifestyle of mankind. The lockdown has brought the life to a standstill. It has been responsible for shattering economies, loss of jobs, interruption in education, change in lifestyle and dietary pattern and a host of other changes. The intense lockdown period starting from March to June, 2020 has been responsible for limiting the ways of human interaction and socialization too, which is not normalized till now. These changes in lifestyle, human social interactions and change in work-pattern have influenced the psychological well-being of the individuals too. The psychological impact of COVID-19 has been well documented in a number of studies done in India or abroad[1-3].

Medical education is considered to be one of those education streams requiring constant studies, practice and honing of skills. However, COVID-19 has jolted the medical education system very adversely, particularly the undergraduate studies where students had to go on a forced vacation owing to outbreak of COVID-19. This forced vacation was an unwarranted interruption in the ongoing medical studies, breaking the schedule of medical studies and its continuity has resulted into a psychological stress and anxiety among the affected medical students[4-6].

A significant association between psychological stress and anxiety with menstrual irregularities among women in different age groups has been reported in literature[7-9]. An association between psychological stress and anxiety with menstrual irregularities has already been reported in different context[9]. Considering the fact that undergraduate medical undergraduate students are already under tremendous psychological stress and anxiety owing to

this unwarranted forced vacation that has affected their study schedule as well as has resulted in a lot of uncertainty, the present study was planned with an aim to study the impact of COVID-19 related stress and anxiety on the menstrual pattern of undergraduate medical students.

MATERIAL AND METHOD

A total of 126 female MBBS students (I-IV semester students) on forced vacations as a result of COVID-19 outbreak and subsequent lockdown studying in different medical institutions across India were contacted telephonically or through e-mail between July, 2020 to August, 2020.

They were enquired regarding changes in menstrual pattern during the lockdown period (March 23 to June 30). The changes in menstrual pattern were categorized under five categories – heavy bleeding, fluctuations intermenstrual interval, fluctuation in cycle length, scanty flow and no change respectively.

The participants were also evaluated for level of anxiety. Level of anxiety was evaluated using Hospital Anxiety and Depression Scale (HADS). HADS score 0-7 were taken as normal, 8-10 as borderline and >10 as abnormal respectively.

Data was analyzed using SPSS 15.0. Chi-square test was used to compare the data.

RESULTS

Age of participants ranged from 17 to 22 years. Mean age of participants was 20.29±1.88 years. Almost half (n=62; 49.2%) girls reported of menstrual disturbances. Maximum (n=31; 24.6%) reported of flucation in intermenstrual intervals (short / prolonged) followed by those reporting heavy bleeding (n=12; 9.5%), fluctuation in length of menstrual cycles (short / prolonged) (n=11; 8.7%) and scanty flow (n=8; 6.3%) respectively. On administration of HADS, 53 (42.1%) had scores indicating abnormality (HADS score >7) - A total of 23 (18.3%) had significant anxiety (HADS score >10) while 30 (23.8%) had borderline anxiety (HADS score 8-10) (Table 1).

Table 1: Characteristics of MBBS Freshers (I-IV) Semester

SN	Characteristic	Statistic
1.	Mean Age±SD (Range) in years	20.29±1.88 (17-22)
2.	Disturbed menstrual pattern	62 (49.2%)
	Heavy bleeding	12 (9.5%)
	Fluctuation in intermenstrual interval	31 (24.6%)
	Fluctuation in cycle length	11 (8.7%)
	Scanty flow	8 (6.3%)
3.	HADS Scores	
	0-7 – Normal	73 (57.9%)
	8-10 – Borderline	30 (23.8%)
	>10 – Abnormal	23 (18.3%)

Prevalence of anxiety was significantly higher in girls experiencing changed menstrual patterns (69.4%) as compared to those having normal menstrual pattern (13.7%) ($p<0.001$) (Table 2).

Table 2: Association between change in menstrual pattern and anxiety

SN	Menstrual pattern	HADS Scores		Total
		Abnormal (8 or above) (n=53)	Normal (0-7) (n=73)	
1.	Disturbed	43 (69.4%)	19 (30.6%)	62
2.	Normal	10 (15.6%)	54 (84.4%)	64
	Total	53	73	126

$\chi^2=37.3$; $p<0.001$; *Percentages have been calculated row-wise*

DISCUSSION

COVID-19 has been responsible for generating stress and anxiety in general population as well as aspiring professionals like medical students[3-6]. The uncertainties associated with COVID-19 lockdown period, interruption in study schedule, broken social ties and changes in day-to-day lifestyle have resulted in a lot of stress and anxiety in these patients. In present study, we found that there was a high prevalence of borderline to marked anxiety (42.1%) in girl undergraduate medical students. High prevalence of anxiety among medical students as a result of COVID-19 outbreak has been reported in other studies too. In a recent meta-analysis, Lasheras *et al.*[10] reported the prevalence of anxiety in different reviewed articles to range from 17.1% to 46.1% with a pooled prevalence of 28%. In present study, we had used HADS and while calculating the prevalence of anxiety we included borderline anxiety too in the abnormal category and hence the proportion of those with anxiety is slightly higher. As such, 18.3% students in our study had significant anxiety. The reason for overall high prevalence of anxiety in our study could also be owing to inclusion of girl students only. Gender differences in prevalence of anxiety have been reported in earlier studies and it has been reported to be higher in girls as compared to boys[9].

In present study, we found that almost half (49.2%) girls experienced medical irregularities. Increase in prevalence of menstrual irregularities among women as a result of COVID-19 pandemic has also been reported by Yuksei and Ozgor[11] who reported more than two-fold rise in prevalence of menstrual irregularities among women during the COVID-19 pandemic. Irregular periods and severe menstrual cramps have been reported by women in different health surveys too[12]. In present study we observed a high prevalence of menstrual irregularities among undergraduate medical students along with a high prevalence of anxiety too.

A relationship between psychological stress and anxiety and menstrual problems has also been

reported in different studies[7-9]. In present study we found a significant association of anxiety with menstrual irregularities in medical undergraduates results and thus could link the high prevalence of menstrual irregularities with COVID-19 generated anxiety and stress.

The findings of present study indicate the need for psychological interventions, evolution of newer coping strategies to cope up with the stress and anxiety related with such unforeseen circumstances like COVID-19. Despite having a serious adverse impact on health and economy, COVID-19 has given an opportunity to understand the gaps in our social and financial milieu and thus evolve newer strategies to cope-up with the tremendous pressures of such unforeseen circumstances. Further studies on this aspect are warranted.

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UG-Original Article

SLEEP PATTERN OF UNDERGRADUATE MEDICAL STUDENTS DURING COVID-19 VACATIONS (MARCH-AUGUST, 2020)

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ABSTRACT

Aim: Forced vacactions during COVID-19 outbreak have disrupted the studies and normal routine of undergraduate medical students. In this study we made an attempt to study the changed sleep pattern of undergraduate medical students during COVID-9 vacations. **Material and Method**: A total of 111 undergradute MBBS students (II to VI semester) studying in different medical institutions across India were contacted telephonically or through electronic mail. The pattern of sleep (duration, daytime sleep, night time sleep, continuous sleep, broken sleep) was studied. The sleep quality was assessed using Epworth Sleepiness Scale. **Results**: Age of students ranged from 18 to 24 years. Majority of them were girls (58.6%). Total sleep duration was reported to be <6 hrs by 18 (16.2%), 6-8 hrs by 22 (19.8%), 8-10 hrs by 50 (45.0%) and >12 hrs by 21 (18.9%) students respectively. A total of 62 (55.9%) students reported of sleeping more than 4 hrs a day between 9a.m. to 6p.m. On administering Epworth Sleepiness Scale, only 25 (22.5%) had normal sleep pattern. Mild, moderate and severe sleepiness was reported by 19 (17.1%), 54 (48.6%) and 13 (11.7%) students respectively. **Conclusion**: COVID-19 has affected the sleep pattern of undergraduate medical students adversely and resulted in a high proportion of disordered sleep.

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Key Words: COVID-19, Sleep Pattern, Undergraduate Medical Students, Epworth Sleep Scale

INTRODUCTION

The importance of sleep in maintenance of good health is well documented and cannot be denied. Sleep is essential for maintenance of health and wellbeing. promoting growth, learning and cognitive development. It holds an important place in stimulating immunity and has a important role in determining the cardiovascular health[1,2].

The sleep schedules are normally affected by lifestyle and pattern of daytime and nocturnal activities of an individual. Undergraduate medical students, in their normal routine spend 6 to 8 hours in campus and 2 to 4 hours of off-campus studies. Campus life is buzzed with a lot of physical activity too. Moving from the hostel to the campus and from one lecture theatre to another, from one lab to another are the minimal physical activities performed by these students. Apart from this, participation in sports, physical exercise, moving around the campus with friends are some of the other activities in which these students participate and accordingly set their sleep-schedule.

The outbreak of pandemic COVID-19 in India and subsequent lockdown starting from March, 2020 has led to disruption of normal routine of almost all the individuals, medical students being no exception. This resulted in a disruption of studies, normal routine and physical activity profile of these students, resulting in a change in sleep pattern in view of the changed schedule of individuals.

In present study, we made an attempt to study the changed sleep pattern and related sleep disorders in undergraduate medical students on forced vacation from March, 2020 to August, 2020.

MATERIAL AND METHODS

A total of 150 undergraduate medical students (II to VI semester) were contacted telephonically or through electronic mail in the last week of August regarding their sleep pattern during COVID-19 vacations using a structural questionnaire prepared for the purpose. The students were enquired about average duration of total sleep per day, duration of daytime sleep, duration of night time sleep and disruptions/break in sleep. The sleep quality of students was assessed using Epworth Slepiness scale. Epworth sleepiness scale is an eight item simple scale that assesses the chances of being dozed off or fallen asleep while engaged in normal life activities . For each item one has to score from 0 to 3, with 0 representing would never doze, 1 representing slight chance of dozing, 2 representing moderate chance of

dozing and 3 representing high chance of dozing respectively. A total score ≤10 represents normal sleepiness, 11 to 14 represents mild sleepiness, 15 to 17 represnts moderate sleepiness and 18 to 24 representing severe sleepiness. Finally complete responses were obtained from 111 students and were tabulated and analyzed.

RESULTS

Complete responses were obtained from 111/150 (74.0%) students. Age of respondents ranged from 18 to 24 years with a median value of 20 years. Majority of respondents were females (59.6%). Maximum respondent reported of sleeping 9-12 hrs per day (45%) followed by those sleeping for 6-8 hrs (19.8%), >12 hrs (18.9%) and <6 hrs (16.2%) respectively. Daytime sleep >4 hrs was reported by 62 (55.9%) respondents. Most of the students (80.2%) reported no fixed time for going to bed. A total of 47 (42.3%) reported of disrupted/ broken sleep. On administering Epworth Sleepiness Scale, only 25 (22.5%) had normal sleep pattern. Mild, moderate and severe sleepiness was reported by 19 (17.1%), 54 (48.6%) and 13 (11.7%) students respectively (Table 1).

Table 1: General Profile and Sleep Characteristics of Undergraduate Medical Students during COVID-19 lockdown phase (March 2020-August 2020)

Median age (Range)	20 (18-24)
Male: Female	46 (41.4%): 65 (59.6%)
Total sleep duration	
<6 hrs	18 (16.2%)
6-8 hrs	22 (19.8%)
9-12 hrs	50 (45.0%)
>12 hrs	21 (18.9%)
Daytime sleep >4 hrs	62 (55.9%)
No fixed time for going to bed	89 (80.2%)
Disrupted/Broken sleep	47 (42.3%)
Sleepiness (as per Epworth sleep scale)	
No sleepiness	25 (22.5%)
Mild sleepiness	19 (17.1%)
Moderate sleepiness	54 (48.6%)
Severe sleepiness	13 (11.7%)

DISCUSSION

In present study, majority of students reported of sleep duration ≥9 hrs (n=71; 64.0%). This is substantially more than the average sleep duration of MBBS students as reported by Chutani *et al.*[3] and Israel *et al.*[4] who reported it to be 6.38 and 6.12 hrs respectively and placed majority of students in short sleepers category. The effect of COVID-19 seems to have reflected in terms of an opportunity to fill that gap of short sleep with relatively prolonged sleep. However, the pattern of sleep in present study reflected some problematic areas too. One of these was excessive daytime sleep as reflected by >4 hrs daytime sleep by 62 (55.9%) students. Moreover, a substantial number of students (16.2%) also reported of short sleep (<6 hrs), thus COVID-19 seems to have affected the sleep pattern in both the extreme directions. A high proportion of students reporting sleep disruptions (42.3%) and report of no fixed time for going to bed by most of the students (80.2%) students showed that the COVID-19 has disrupted the sleep schedule adversely. This adverse impact was measured in terms of sleepiness as denoted by Epworth sleepiness scale with only 22.5% students reporting a normal score. The findings in the present study are in agreement with the observations of Romero-Blanco *et al.*[5] who also reported that although students spent more time in bed, overall sleep quality was worse during lockdown. A study conducted by Li *et al.*[6] showed that the prevalence of insomnia increased significantly during the COVID-19 outbreak (in some cases new onsets of insomnia), that time in bed (TIB) and total sleep time (TST) increased, and that sleep efficiency significantly decreased. In another study, Marelli *et al.*[7] also reported poor sleep quality among University students during COVID-19 lockdown period and attributed it to possible role of depression and anxiety in the students. The prolonging of lockdown in phases, loss of studies, disruption from normal routine have multiple psychosomatic effects and we also feel it to be responsible for changes in sleep pattern and sleep quality in undergraduate students.

The findings of present study showed that COVID-19 has affected the life in multiple ways. Accepting that we have to live up with COVID-19 for a long period, it is essential that alternate lifestyle strategies should be evolved and adopted in day-to-day life in order to minimize the confounding effect of COVID-19 in life.

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